Incidence and determinants of failure of the initial highly active antiretroviral therapy (HAART) regimen in a cohort of ART naïve HIV infected south Indian adults

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M.D (General Medicine) Examination of the Tamil Nadu

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To be held in 2007.

C E R T I F I C A T E

This is to certify that the dissertation entitled *"Incidence and determinants of failure of the initial highly active antiretroviral therapy (HAART) regimen in a cohort of ART naïve HIV infected south Indian adults"* is the bonafide original work of Dr. Ajith Sivadasan towards the M.D. Branch-1 (General Medicine) Degree Examination of the Tamil Nadu Dr. M.G.R University, Chennai to be conducted in 2007.

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C O N T E N T S

LIST OF ABBREVIATIONS AND ACRONYMS

ABC : **Abacavir**

ACTG : **AIDS Clinical Trials Group**

ADR : **Adverse Drug Reaction**

AIDS : **Acquired Immunodeficiency Syndrome**

ALC : **Absolute lymphocyte Count**

ALT : **Alanine aminotransferase**

ART : **Anti-Retroviral Therapy**

ARV : **Anti-Retroviral**

AST : **Aspartate aminotransferase**

AZT : **Azidothymidine**

BMI : **Body Mass Index**

CBC : **Complete Blood Counts**

CD4 : **CD4+ T-Lymphocyte (T-lymphocyte bearing CD4 receptor)**

CI : **(95%) confidence interval**

ddI : **Didanosine**

d4T : **Stavudine**

DRESS : **Drug Rash, Eosinophilia and Systemic Symptoms**

EFV : **Efavirenz**

FDC : **Fixed-Dose Combination**

FTC : **Emricitabine**

HAART : **Highly Active Anti-Retroviral Therapy**

HBV : **Hepatitis B Virus**

HCV : **Hepatitis C Virus**

HIV : **Human Immunodeficiency Virus**

IDV : **Indinavir**

IGT : **Impaired Glucose Tolerance**

IQR : **Inter-Quartile Range**

IRIS : **Immune Reconstitution Inflammatory Syndrome**

MTCT : **Mother- to- Child Transmission**

NACO : **National AIDS Control Organization**

NFV : **Nelfinavir**

NNRTI : **Non Nucleoside Reverse Transcriptase Inhibitor**

NRTI : **Nucleoside Reverse Transcriptase Inhibitor**

NtRTI : **Nucleotide Reverse Transcriptase Inhibitor**

NVP : **Nevirapine**

OI : **Opportunistic Infection**

PI : **Protease Inhibitor**

PLHA : **People Living with HIV/AIDS**

PPTCT	**: Prevention of Parent - to - Child Transmission**
PVL	**: Plasma Viral Load**
RIF	**: Rifampicin**
SJS	**: Stevens-Johnson Syndrome**
STI	**: Sexually Transmitted Infections**
TB	**: Tuberculosis**
TDF	**: Tenofovir**
TEN	**: Toxic Epidermal Necrolysis**
3TC	**: Lamivudine**
UNAIDS	**: United Nations Programme on HIV/AIDS**
VCTC	**: Voluntary Counseling and Testing Centre**
WHO	**: World Health Organization**
YRG CARE	**: Y R Gaitonde Centre for AIDS Research and Education**

INTRODUCTION

The battle against the staggering worldwide growth of the HIV pandemic has been revolutionalised by the advent of HAART. HAART has resulted in substantial reductions in mortality, progression to AIDS, incidence of OIs, and hospitalizations in patients who respond to therapy.**(1)** With rational use of HAART, HIV infection can be transformed into a chronic manageable illness like diabetes and hypertension. Pallela et al in a study published in 1998, provided evidence of a massive decrease in morbidity and mortality associated with HIV infection after the advent of HAART. Mortality rates had decreased by 75% (from 35.1 to 8.8 per 100 person-years) between early 1994 and mid-1997, and the incidence of AIDS-defining diseases decreased by nearly 73%.**(2)** Similar efficacy was noted by Egger et al in the ART collaboration cohort study.**(3)** It provided important clinical implications for management which were subsequently incorporated in the treatment guidelines.

Majority of people infected with HIV reside in the developing world where resources are limited. Ensuring universal access to HAART is critical for the survival of patients in these settings. This problem has been partly overcome by the programmes and initiatives launched by the various health organizations. In the **"3 by 5"** initiative, launched by WHO in 2003, a **global target** was set to provide three million individuals living in the developing world with ART, by 2005. As part of the world AIDS day commemoration in

2003, the Government of India (GOI) announced a policy commitment to provide free ART to one lakh patients by the year 2007 and 1.8 lakh patients by 2010. This policy development was in line with the declaration of the AIDS treatment gap as a global public health emergency and the launch of the **"3 by 5"** initiative by WHO. The national ART programme has also been scaled-up with centers providing comprehensive HIV/AIDS continuum of prevention, care and treatment services.

Generic FDC of ARV drugs manufactured mostly by Indian pharmaceutical firms have given a boost to efforts to improve access to HAART. The advantages of using generic fixed combination HAART include: low cost, simplified education and training of providers, standard monitoring for toxicity, predictable pattern of resistance, better adherence and limited number of drugs to manage with easier organization of support groups.

However, there are scarce data on the efficacy and tolerability of antiretroviral therapy in Indian population. Pujari et al while studying the effectiveness of generic NVP-based HAART in India concluded that there was a significant improvement in CD4 cell counts over a period of 2 years with this regimen. The incidence of acute NVP induced ADR like drug rash and hepatitis were 6.6% and 3.2% respectively.**(4)** The lower incidence was attributed to adherence to the lead-in-dose of NVP and monitoring of liver function tests only when clinically indicated. Kumarasamy et al of YRG CARE centre, Chennai identified modification of generic initial HAART regimens in 20% of the patients with ADR contributing to nearly 64% of treatment modification.**(5)**

Due to noticeable differences in the demographic profile of the patients, results of studies from the West may not be directly applicable to our population. There are reasons to believe that response to HAART in our patients may be significantly different from the West.

The factors that could potentially modify the response to HAART in India compared to the West include:

1. Presentation at fairly advanced stages of HIV infection.
2. High prevalence of *Mycobacterium tuberculosis* co-infection (Nearly two million of the five million HIV infected adults in India are co-infected with TB).**(6)**
3. Use of thymidine analogue NRTI and NVP in HAART regimens.
4. Increased prevalence of malnutrition and IGT (impaired glucose tolerance).
5. The presence of non-subtype B HIV virus (subtype C).**(7)**

Hence, the present study was designed to find the incidence and determinants of failure of the initial HAART regimen in a cohort of ART naïve south Indian adults.

Optimization of the initial HAART regimen for complete viral suppression and better tolerability is paramount for the prognosis of HIV infected patients. In order to choose the optimal regimen one should also be fully aware of the concepts of HAART and the pharmacology of individual ARV drugs.

OBJECTIVES OF STUDY

1. To prospectively follow-up a cohort of antiretroviral therapy naïve HIV infected South Indian adults started on Highly Active Antiretroviral therapy (HAART).
2. To determine the incidence and determinants of failure of initial HAART regimen in these patients.
3. To determine the incidence and predictors of severe adverse drug reactions (ADR) necessitating a change of the HAART regimen in the study cohort.

Review of Literature

HIV medicine is a rapidly changing specialty necessitating periodic updating. According to UNAIDS,**(8)** India has 5.7 million people living with HIV - more than any other country in the world. Of these, 39% are females and 30% are below the age of 30 years. According to estimates, it has been projected that India will suffer 12.3 million AIDS deaths during the years 2000-2015. In contrast to the earlier days of the HIV epidemic, a diagnosis of HIV infection need no longer be equated with an inevitably fatal disease. HAART has emerged the cornerstone of management of patients with HIV infection. The appropriate use of potent HAART regimens and other treatment and prophylactic interventions are of critical importance in providing each patient the best opportunity to live a long and healthy life.

Our main focus in this section will be to discuss the factors that could lead to failure of the initial HAART regimen quoting references from published literature in detail and to help formulate measures that could minimize the incidence of regimen failure and increase the tolerability and effectiveness of HAART. To achieve this one has to be aware of the goals of therapy, basic concepts of HAART, exact indications for initiation of therapy and pharmacology of the ARV drugs.

Pathogenesis:

HIV targets, infects and incapacitates cells central to host defenses against microbial pathogens. There is a relentless and high rate of viral replication, progressive decline in CD4+ T cells ('helper' T cells) with profound immunodeficiency and subsequently general decline in health leading to opportunistic infections and cancers.

The following are the goals of antiretroviral therapy:

1. Maximum and durable suppression of viral replication.
2. Preservation and/or restoration of immune functions.
3. Reduction of HIV related morbidity and mortality.
4. Improvement of quality of life.

Concept of HAART:

In addition to achieve the above goals, the concept of HAART has also evolved to prevent the emergence of drug resistant mutants. HAART regimens have at least three active antiretroviral medications. Regimens commonly have a base and a backbone. The base is either an NNRTI or a PI *(there may be a second PI given to "boost" the base PI). The backbone typically consists of two NRTIs.

Note*: PI based regimens frequently use a low dose of Ritonavir to increase ("boost") the drug level and duration of another PI. Ritonavir is an extremely potent inhibitor of PI metabolism via the CYP3A4 pathway.

Evolution of antiretroviral therapy:

The evolution of ART began in 1987 with the advent of AZT monotherapy. Fischl et al demonstrated that AZT administration decreased mortality and the frequency of opportunistic infections in patients with AIDS or AIDS-related complex.**(9**) Hammer et al concluded in his study published in 1997 that addition of another NRTI to AZT significantly slowed the progression of HIV infection and was superior to monotherapy. **(10)** The concept of HAART came in 1997 when Gulick et al demonstrated that with addition of indinavir (IDV) to a dual nucleoside backbone there was durable virological suppression.**(11)**

Impact of therapy:

Advent of HAART resulted in a dramatic decrease in the morbidity and mortality related to HIV infection which has been proven in various studies. A report from HIV clinics in eight cities in the United States conducted by the HIV Outpatient Study (HOPS) showed that the mortality of patients with a CD4 cell counts below 100cells/µL declined from 29.4 per 100 person-years in 1995 to 8.8 per 100 person-years in 1997.**(2)** There was also decline in the three major OIs *Pneumocystis* pneumonia, *Mycobacterium avium* bacteremia, and disseminated cytomegalovirus infections; these declined during this period from 21.9 to 2.3 per 100 person-years. The EuroSIDA cohort showed a dramatic decline in mortality from 23.3 per 100 person-years in 1994 to 4.1 per 100 person-years in 1998.**(12)**

Challenges to antiretroviral therapy

The new concerns that arose in due course of time to continuation of a successful HAART regimen include:

1. Cost of therapy.
2. Side effects of medications.
3. Drug interactions.
4. Difficulties in adhering to complicated regimens.
5. Emergence of drug resistance
6. Variations in individual response.

Adherence, drug toxicities and emergence of resistance in clinical practice are major issues leading eventually to regimen failure. These will be mentioned in detail in the sections below.

Initiation and monitoring of patients on HAART

Indications for antiretroviral therapy:

The major factors used to indicate a need for initiation of ART in patients are the presence of symptomatic HIV disease and the CD4 cell counts. There is strong evidence supporting the use of the CD4 cell counts as the major determinant in initiating therapy. **(2,13)** The plasma HIV RNA level remains an independent predictor of clinical outcome in patients who do not receive HAART and is one of the best available guides for monitoring the effectiveness of HAART.**(14,15)**

Several observations contribute to the dilemma about when to start treatment in asymptomatic individuals. Antiretroviral therapy with a CD4 cell counts > 200/µL has either no, or only a modest benefit in some studies, while others shows substantial benefits.**(16**)

Although the rate of disease progression among HIV-infected individuals varies greatly, whenever possible, HAART should be initiated before the CD4 threshold of 200/µL has been reached. Patients with CD4 cell counts < 200/µL are at greatly increased risk of serious life-threatening OIs**,** and immune reconstitution illness is largely limited to individuals who initiate therapy with very low CD4 cell counts and very high plasma viral loads.(**17-19**) Individuals with CD4 cell counts > 350/µL, on the other hand, have a low risk of clinical progression at 3 years, and concerns about the impact of ARV drugs on quality of life, adherence to regimens, risks of serious adverse effects of the drugs, and emergence of viral resistance that will limit future treatment options generally outweigh the benefits of durable viral suppression. No study has shown convincing evidence of benefit for treatment initiated when the CD4 count is > 350/µL.

In patients with a CD4 cell counts between 200 and 350/µL, clinicians must consider the potential risks and benefits of treatment since current drugs have substantial short- and long-term toxicity and carry risk of emergence of drug resistance if inadvertently used.

Viral load is also an independent prognostic indicator. Extremely high viral loads (>100,000 copies/mL) correlate with a poor prognosis and is an indicator for initiation of treatment.

The following are the recommendations for initiating ART in adults with HIV infection (*WHO 2003*)

If CD4 cell testing available:

WHO clinical stage IV disease.

WHO clinical stage III with consideration of using CD4 cell counts < 350/µL to assist decision making.

WHO clinical stage I or II disease with CD4 cell counts less than or equal to 200/µL

If CD4 testing not available:

WHO clinical stage III and IV disease

WHO stage II disease with absolute lymphocyte count (ALC) less than or equal to 1200 cells/µL.

In addition to them, patients with acute HIV infection may be candidates for ART as they can decrease severity of acute disease and reduce disease progression/transmission rates. Pregnant women should also generally be treated with ART to reduce the risk of vertical transmission (PPTCT)

Evaluation prior to initiation of ART

1. Confirmation of diagnosis: A prerequisite prior to HAART initiation. It is also needed to rule out HIV-2 infection as NNRTIs have no activity against HIV-2.**(20)**

2. History and physical examination**:** should focus on symptomatic HIV disease for staging of infection, evidence of OI that could potentially flare with the immune reconstitution seen after starting HAART.

3. As adherence is probably the most important factor in determining the success of an initial HAART regimen, a detailed psychosocial evaluation is required as these factors can have a strong influence on patient adherence.

Psychosocial evaluation —Issues to consider include:

1. Substance abuse: Substance abuse contributes to a disordered lifestyle and may lead to inadvertent missed medications doses.

2. Psychiatric disorders: Depression, bipolar disorder, and other psychiatric disorders may interfere with a patient's ability or desire to adhere to a medication regimen.

3. Housing: Patients with an unstable housing situation (such as the homeless) may have difficulties keeping medications available, remembering to take medications, and dealing with side effects such as diarrhea.

4. Ability to afford medications: Depending on where patients live, their economic resources, and their insurance, affordability of medications may be a major constraint in some cases.

5. Work schedule: Patients with irregular work schedules may have difficulty taking medications at prescribed times.

6. Family support and friends.

All patients being considered for ART should have the following laboratory tests:

1. Complete blood count with differential.

2. Electrolytes, serum creatinine, and glucose.

3. Liver function tests.

4. A lipid profile including triglycerides.

5. Serologic tests for hepatitis B and hepatitis C virus.

Measurement of the HIV plasma viral load and CD4 cell counts (preferably when patient not ill)

ANTI-RETROVIRAL REGIMENS:

Main classes of drugs used:

- Nucleoside (and nucleotide) reverse transcriptase inhibitors (NRTIs)
- Nonnucleoside reverse transcriptase inhibitors (NNRTIs)
- Protease inhibitors (PIs)
- Nucleotide analogue reverse transcriptase inhibitors (NtRTI like tenofovir)
- Fusion inhibitors

Fusion inhibitors are not currently used as part of initial ART regimens.

Pill burden - HAART regimens, particularly those that include PIs, frequently require patients to ingest many large pills with each dose. Newer drugs, regimens, and pill formulations are reducing this burden.

Drug regimens:

Major clinical trials of HAART are still underway. Four drug regimens and sequential three drug regimens could prove to be more potent and tolerable

PI plus NNRTI based regimens:

ACTG 384 (AIDS Control Trial Groups)— This randomized trial compared a four-drug regimens containing (NFV + EFV + 2 NRTIs) versus three- drug regimens (NFV or EFV with 2 NRTIs) comparing NFV with EFV. The NRTI backbone of (AZT + 3TC) was compared to (d4T + ddI). The conclusions of the trial were:

a) There were no differences between the four-drug and sequential three drug regimens in the primary end points.

b) EFV was better than NFV when combined with AZT + 3TC.

Hence, it was concluded that AZT + 3TC + EFV was the preferred initial HAART regimen.**(21)**

Comparison of NNRTI based regimens:

In the 2NN study, Van Leth et al concluded that HAART with either NVP or EFV combined with a standard dual nucleoside backbone showed similar efficacy with some

noticeable differences in safety profile. The NVP once daily group had significantly higher incidence of side effects. The combination of both EFV and NVP was neither effective nor tolerated in the study population.**(22)**

Tenofovir based regimens

Tenofovir disoproxil fumarate (TDF), a NtRTI is a potent agent with a long intracellular half-life that allows for once-daily dosing. It has been well tolerated in clinical trials, without evidence of the mitochondrial toxicity that has been associated with long-term treatment of some of the NRTIs. Because of its demonstrated efficacy and favorable safety profile, TDF has quickly become a favored nucleoside component of ARV regimens for both treatment-naive and -experienced patients.**(23)**

Antiretroviral combinations to avoid — certain combinations of ARV medications that might appear to fit into a standard pattern should be avoided either because of toxicity or lack of efficacy:

- AZT and d4T should not be used together as their actions are antagonistic.
- 3TC and FTC are similar drugs and should not be used together.
- The use of EFV and NVP together produces more side effects and is less efficacious than either drug alone (2NN study)
- Because of concern about the long-term toxicity of ddI with d4T including peripheral neuropathy, pancreatitis and lipodystrophy this combination is less desirable.

Laboratory monitoring

- CBC with differential
- Electrolytes
- Serum creatinine and blood urea nitrogen (BUN)
- Liver transaminases

Patients on NVP should have liver transaminases monitored more frequently initially (at baseline, two weeks). Lipid and glucose levels should be monitored at baseline, three months, six months, and then yearly for protease inhibitor based regimens..

There is also need for periodic monitoring of plasma viral load and CD 4 cell counts while on therapy. These aspects will be described in detail below.

Indications for changing therapy

Major factors contributing to the durability of an initial regimen include antiviral potency of regimen, adherence, tolerability, convenience of the regimen, and baseline virologic or immunologic status. The four common indications for changing the antiretroviral regimen based on previous studies **(24-26)** include:

- Toxicity
- Treatment failure
- Difficulty adhering to the regimen
- Current antiretroviral regimen is suboptimal

In the Swiss HIV Cohort Study, Fellay et al described that 47% of patients on potent HAART had clinical adverse events and 27% had laboratory adverse events that were considered to be probably or definitely attributable to therapy.**(27)** In another US based ART naïve cohort of 3414 patients with a median follow-up of 211 days, Yuan et al documented that 628 patients (18.4%) reportedly discontinued the HAART regimen because of drug toxicity, 456 patients (13.4%) because of non-compliance, and 257 (7.5%) because of treatment failure.**(26)**

Antiretroviral treatment failure: defined as a suboptimal response to therapy and is often associated with virologic failure, immunologic failure, and/or clinical progression. **ART may need to be changed because of either treatment failure or toxicity.** Treatment failure can be evaluated clinically, immunologically by measurement of the CD4 cell counts, and/or virologically by measuring viral loads. However, as the latter are not normally available in resource-limited settings like ours, **it is recommended that programmes in such settings should primarily use clinical criteria and, where possible, CD4 cell counts, to define treatment failure.**

Factors increasing the likelihood of treatment failure based on previous studies have been: baseline patient factors such as earlier calendar year of starting therapy, higher pretreatment or baseline HIV RNA level (depending on the specific regimen used), lower pretreatment or nadir CD4 cell counts, prior AIDS diagnosis, co-morbidities (e.g. depression, active substance use), presence of drug resistant virus, prior treatment failure with development of drug resistance or cross resistance, non-adherence, drug toxicity and interactions.**(25)**

Incomplete virologic response is defined as repeated HIV RNA > 400 copies/mL after 24 weeks or >50 copies/mL by 48 weeks in a treatment-naïve patient initiating therapy. Baseline HIV RNA may impact the time course of response and some patients will take longer than others to suppress HIV RNA levels. The timing, pattern, and/or slope of HIV RNA decrease may predict ultimate virologic response. For example, most patients with an adequate virologic response at 24 weeks had at least a 1 log10 copies/mL HIV RNA decrease at 1-4 weeks after starting therapy.**(28)**

Blips — this term refers to intermittent periods of "detectable viremia" meaning viral loads >50 copies/mL. These are common and do not predict subsequent virologic failure. They do not require intervention with a new regimen unless the viral load is sustained at >50 copies/mL or perhaps >400 copies/mL.**(29)**

Cross Resistance. ARV drug resistance is a consequence of mutations in viral proteins targeted by the ARV agents. Another contributing factor is the extensive genetic diversity of HIV-1 with high rates of viral replication and highly error prone reverse transcriptase enzyme. The estimated prevalence of mutations conferring resistance to NRTIs was 7.8 %, and the prevalence was 3 % for NNRTIs and 0.7% for PIs according to Novak et al. **(30)** Cross-resistance among NRTIs is common but varies by drug. Most, if not all, NNRTI-associated resistance mutations confer resistance to the entire NNRTI class of drugs because the development of a single mutation, such as the K103N mutation, results in drug resistance**.** They also have a very low genetic barrier to development of resistance.

The following are the guidelines for changing an antiretroviral therapy regimen for virological failure:

1. A detailed treatment history and past and current resistance test results to identify active agents (preferably 3 or more) to design a new regimen. In general, one active drug should not be added to a failing regimen because drug resistance is likely to develop quickly

2. For the patient with virologic failure, one needs to perform resistance testing while the patient still is taking the drug regimen or within 4 weeks after regimen discontinuation .

3. If three active agents cannot be identified, one needs to consider pharmacokinetic enhancement of protease inhibitors (with the exception of NFV) with Ritonavir and/or re-using other prior antiretroviral agents.

4. Adding a drug with a new mechanism of action (e.g. HIV entry inhibitor) to an optimized background antiretroviral regimen can add significant antiretroviral activity. **(31)**

5. Other implications for routine resistance testing prior to initiation of antiretroviral therapy include chronically infected ART naïve individuals with spouse on antiretroviral therapy and in some cases of acute HIV infection.

Immunologic Failure

Immunologic failure can be defined as a drop of greater than 30 % in CD4 cell count from peak value or a decrease to below the baseline CD4 cell count on therapy.**(32)** Mean

increases in CD4 cell counts in treatment-naïve patients with initial antiretroviral regimens are approximately 150/µL over the first year. Immunologic failure may not warrant a change in therapy in the setting of suppressed viremia. There is no accepted definition of immunological failure which can be used if CD4 counts are not available.

Clinical Progression

Clinical Progression can be defined as the occurrence or recurrence of AIDS defining opportunistic infections (after at least 3 months on an ARV regimen, when the drugs have been given for a sufficient time). Differentiating clinical failure from immune reconstitution syndromes (which can be seen within the first several weeks after the institution of therapy if a sub clinical infection is present at baseline) can at times be extremely difficult. Changing therapy in setting of IRIS is not warranted. In one study conducted in Netherlands, Ferdinand et al noticed clinical progression (a new AIDS event or death) in 6.3% of patients during a median follow-up of 48 weeks.**(25)**

Changing because of toxicity

In the setting of a good therapeutic response, the development of a clearly definable toxicity permits single drug substitutions without compromising the overall regimen. In respect of other toxicities for which a specific causal agent cannot be identified, and/or of low-grade but intolerable side-effects that frequently compromise adherence, a complete regimen switch may be the ideal approach. If an interruption in therapy is indicated in order to deal with toxicity the entire regimen should be temporarily stopped so as to prevent the emergence of drug resistance.

Main class specific toxicities of ART are as listed:

1. NNRTI: hypersensitivity.

2. NRTI: mitochondrial toxicity.

3. PI: metabolic disorders.

4. NtRTI: proximal renal tubular dysfunction.

Skin rash:

NVP-associated rash develops in about 17% of patients, with serious, i.e. grade 3 or 4, rash requiring treatment discontinuation in about 6-8%. There does not appear to be cross-reactivity for rash between EFV and NVP.**(33**) Severe life threatening complications including SJS, TEN and DRESS syndrome have been described necessitating permanent discontinuation of the drug. Female gender, plasma HIV RNA load > 10,000 copies/mL, heterosexual transmission and abacavir treatment constitute risk factors associated with risk of rash.**(34**) Use of a two week-lead -in dose escalation schedule while initiating NVP may reduce the incidence of rash. The role of steroids in NVP-associated rash is controversial.**(35)**

Skin rash is also known to occur with abacavir and amprenavir.

Hepatotoxicity:

Hepatotoxicity defined as at least 3-5 times elevation in liver enzymes (ALT/AST/GGT) with or without clinical hepatitis has been reported in patients receiving HAART. Hepatotoxicity can occur in the absence of rash or the hypersensitivity syndrome.

The AIDS Clinical Trials Group (ACTG) has classified laboratory-defined hepatotoxicity based on changes in transaminase levels relative to the upper limits of normal (ULN):

Grade 0 (less than 1.25 x ULN);

Grade 1 (1.25-2.5 x ULN);

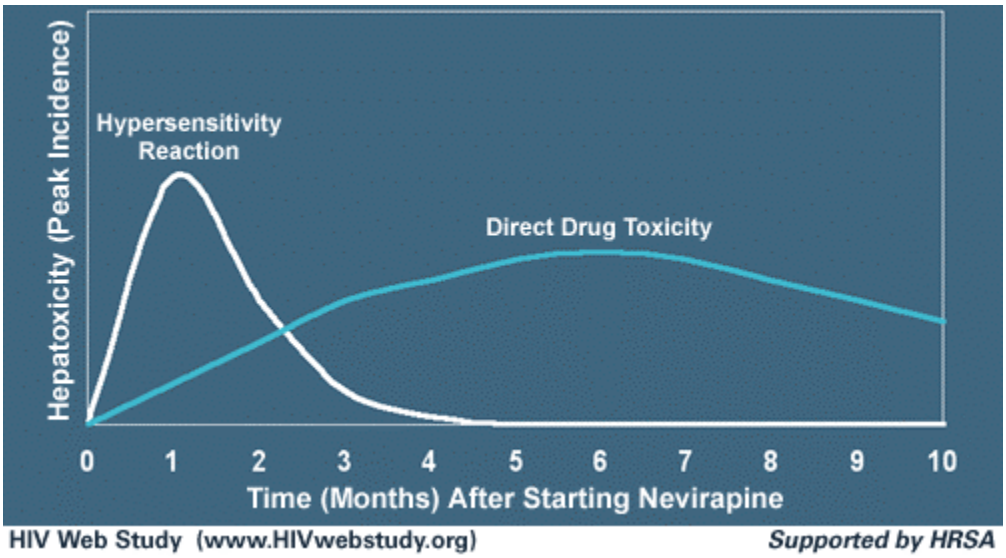
Grade 2 (2.5-5.0 x ULN);

Grade 3 (5.0-10.0 x ULN); and

Grade 4 (greater than 10.0 x ULN)

Pathogenesis:

First, an immune-mediated hypersensitivity reaction can develop within 18 weeks of starting NVP, with most cases occurring between day 10 and 30. Patients with this type of hepatotoxicity typically have concomitant constitutional symptoms that may include fever, skin reactions, malaise, and nausea. The second type typically occurs after 18 weeks of NVP therapy and most likely represents an intrinsic toxic drug effect.



Among persons taking NVP, the incidence of an asymptomatic increase in hepatic transaminase levels is approximately 5-15%, with rates on the lower end of this range reported from studies that defined hepatotoxicity as a five-fold or greater increases in transaminase levels and rates on the higher end in studies that used a cut-off of a three-fold or greater increase.(**36,37)** While most hepatic toxicities occur within the first 12 weeks after the start of therapy, one-third of cases first occur after NVP therapy has been in progress for 12 weeks or more. The incidence of clinically symptomatic hepatitis among persons taking NVP is approximately 1%.

.Identified risk factors for developing hepatotoxicity with NVP consist of female gender, chronic hepatitis C virus infection, chronic hepatitis B virus infection, a CD4 cell count greater than 250 cells/µL prior to starting NVP, and abnormal baseline transaminase levels.**(36-38)** In patients affected by co-infection with hepatitis B or C or having an elevated CD4 cell count, there are data suggesting an immunological component to the

toxicity (IRIS) **NVP should be permanently discontinued in patients with NVP-associated hepatitis**.

NVP should not generally be used as initial therapy in women with a CD4 cell count above 250/µL. Men with CD4 cell counts above 400/µL who are started on NVP may also be at increased risk for asymptomatic transaminase elevations, however most patients are not initiated on HAART at CD4 cell counts this high.

Lactic acidosis/hepatic toxicity:

Asymptomatic low-level hyperlactataemia has been reported in 21% of NRTI-treated patients but is not predictive of lactic acidosis; symptomatic hyperlactataemia is less common and severe lactic acidosis and hepatic steatosis develops in only a minority of patients. Lactic acidosis, the most severe degree of lactic acidemia, consists of venous lactate greater than 2 mmol/L (18 mg/dL) and an arterial pH less than 7.30. Several studies, when taken together, have shown detection of asymptomatic or mildly symptomatic lactic acidemia in 8-21% of patients receiving at least one NRTI.(**39,40)** Lactic acidemia with significant symptoms occurs less frequently, with an estimated incidence of 1.5-2.5% among persons taking NRTIs. Although uncommon, lactic acidosis is associated with a high fatality rate (33-57%). Risk factors include the female gender, a high body mass index, prolonged NRTI use, and, possibly, pregnancy, acquired riboflavin and thiamine deficiency, and d4T use.

Pathogenesis:

The proposed pathway of mitochondrial dysfunction is by inhibition of DNA polymerase gamma causing derangements in the oxidative phosphorylation and lactate homeostasis. In vitro, the order of strength of inhibiting polymerase gamma for the different NRTIs is: ddC >> ddI > d4T ≥ZDV >>> TDF = 3TC = FTC = ABC.**(41)**

The initial symptoms are variable; a clinical prodromal syndrome may include generalized fatigue and weakness, gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal pain, hepatomegaly, anorexia, and/or sudden unexplained weight loss), respiratory symptoms (tachypnea and dyspnea) or neurological symptoms (including motor weakness). Laboratory abnormalities can include hyperlactataemia, increased anion gap, and elevated aminotransferases, creatine phosphokinase, lactate dehydrogenase, lipase and amylase. Microvesicular steatosis is seen on histological examination of the liver. Cases have occurred as early as one month and as late as 20 months after the commencement of therapy.

ART should be discontinued in patients with these symptoms, because otherwise there may be progressive toxicity with severe lactic acidosis and respiratory failure. Symptoms associated with lactic acidosis may continue or worsen following the discontinuation of ART. Therapy is primarily supportive (fluid, bicarbonate administration and respiratory support), although in uncontrolled cases the administration of riboflavin and/or thiamine has been described as beneficial. After the resolution of symptoms, regimens that can be considered for restarting ART include a PI combined with an NNRTI and possibly either

ABC or TDF. Nucleoside analogues are effective in inhibiting HIV replication due to their high affinity for the viral enzyme reverse transcriptase (a viral DNA polymerase).

Drug induced anemia:

AZT therapy is probably the most common cause of anemia in HIV-infected patients. In one of the earliest clinical trials placebo controlled trials with AZT in HIV infection, Richmann et al **(42)** discovered statistically significant reductions in hemoglobin levels in 24% of subjects receiving AZT (1,200 mg per day) following 6 weeks of therapy. Twenty one percent of AZT-treated subjects in the trial required red blood cell transfusions while receiving the drug. Neutropenia was noted in 16 % of the patients. Marrow erythroid hypoplasia, aplasia, and megaloblastic maturation have developed as a result of AZT therapy. Subsequent studies have demonstrated that anemia is less common in patients with relatively less advanced HIV disease and in those receiving reduced dosages of AZT.**(42, 43)** More recent studies of combination antiretroviral therapy have confirmed the relatively low incidence of severe anemia at lower doses of AZT (600 mg daily doses**).(44)**.

Hematological toxicity is dose-related and is more common in patients with advanced HIV disease, low CD4 cell counts and in those receiving concomitant bone marrow suppressive medications, such as ganciclovir, pyrimethamine or hydroxyurea. Other known determinants include patients with low serum vitamin B12 levels, anemia, or low neutrophil counts and concurrent use of acetaminophen.**(42)**

Effective therapy for AZT-induced anemia is available in the form of recombinant human erythropoietin. A double-blind, placebo-controlled study demonstrated that recombinant human erythropoietin (100 units/kg 3 times weekly by intravenous bolus) reduced transfusion requirements of AZT-treated HIV-infected patients whose serum levels of endogenous erythropoietin were less than 500 IU per liter.**(45)**

Peripheral neuropathy :

The primary toxicity associated with stavudine based therapy is peripheral neuropathy, which is dependent on both the dose and the duration of treatment and is more common in patients with advanced HIV disease and those who are being treated with other neurotoxic drugs, including didanosine.. The symptoms usually resolve within 2-3 weeks after the discontinuation of d4T. Rare occurrences of ascending neuromuscular weakness, including respiratory failure and death, resembling Guillain-Barre syndrome, have been reported in patients receiving stavudine; most cases have had concomitant lactic acidosis or hyperlactataemia. This forms one important reason for peripheral neuropathy in HIV infected adult. The exact pathogenesis is not known however could involve drug induced mitochondrial toxicity. Risk factors for developing peripheral neuropathy during nucleoside analogue therapy include low CD4+ cell count (<100 cells/μL), a prior history of an AIDS defining illness or neoplasm, a history of peripheral neuropathy, use of other neurotoxic agents including high alcohol (ethanol) consumption and nutritional deficiencies such as low serum hydroxocobalamin levels.**(46)**

Other toxicities seen:

Efavirenz: central nervous system effects and teratogenicity bone disorders.

Protease inhibitors: insulin resistance/diabetes, hyperlipidaemia, lipodystrophy, hepatitis, increased bleeding episodes in haemophiliacs.

Drug interactions causing inhibition of cytochrome p 450 system causing increased drug level can lead to toxicity especially with boosted protease inhibitor regimen.

Adherence:

Adherence to the regimen is essential for successful treatment and hence has been rightly phrased as the "Achilles heel" of antiretroviral therapy.**(47**) Optimal adherence is the compliance to ART that achieves a sustained plasma drug concentration that will inhibit viral replication. In the treatment of patients with HIV infection or the acquired immunodeficiency syndrome, it is essential to achieve more than 95 % adherence to HAART in order to suppress viral replication and avoid the emergence of resistance. However with the advent of boosted regimens and considering the longer half life of NNRTIs, cut off rates of 90 % can be acceptable.

Adherence rate = (number of pills expected to be taken– number of pills missed x 100)

Number of pills expected to be taken

The adherence rate varies not just between individuals, but also in the same individual over time,**(48)** thus making adherence a variable rather than a stable characteristic of an individual. Most people will exhibit low adherence at some time during this extended therapy. Studies have indicated that at least 95% adherence to ART regimens is optimal, with 95% adherence, viral suppression to below detectable levels occurs in 80%.

However, a fall in adherence to 70% (i.e. 25% less than optimal) drastically decreases viral suppression to 33% (i.e. less than 50% achieved with optimal adherence).**(49)** Also, it has been demonstrated that a 10% higher level of adherence results in a 21% reduction in disease progression.

Measuring adherence in clinical practice is however difficult. Self reporting and pill counts are the simplest ways of assessing adherence to therapy.**(50)** Indirect ways like checking the mean corpuscular volume for patients on AZT could be useful. Adherence is promoted by simplified, well tolerated regimens involving as few pills as possible administered no more than two times a day.

PATIENTS AND METHODS

Study Setting:

The study was conducted in **Christian Medical College Hospital, Vellore,** a 1800 bedded academic medical center in south India.

Eligible subjects were recruited from the 'Infectious Diseases Clinic' (ID Clinic) which is a dedicated outpatient service for PLHA.

The **'ID Clinic'** is manned by staff from the departments of General Medicine and Infectious Diseases, Dermatology and Venereology, Child Health, Obstetrics and Gynecology, Psychiatry, counselors, social workers and pharmacists.

The clinic serves as a "one stop shop" to provide **comprehensive**, holistic care for PLHA. The services offered include:

1. Voluntary confidential counseling and testing (VCCTC) services,
2. Diagnosis, treatment and prevention of sexually transmitted infections,
3. Diagnosis, treatment and prevention of opportunistic infections (OI),
4. Nutritional counseling and interventions,
5. Antiretroviral therapy (ARV pharmacy, dedicated pharmacist, adherence counseling and monitoring),
6. PPTCT of HIV infection programmes,
7. Psychosocial interventions.

The clinic functions once every week. The average attendance is around 100 patients per outpatient clinic. All patients have open access to the clinic and are encouraged to attend the General medicine OPD or the emergency services whenever ill.

Emphasis is placed on continuous patient education, in which medical social workers, specialized in HIV medicine, play a major role.

Study Design:

A **prospective** cohort study

The study design and methods were approved by the Research Committee (Institutional Review Board) of Christian Medical College, Vellore.

Subjects:

The study recruited HIV infected adults attending the Infectious Diseases Clinic.

The subjects were residents of southern Indian states (Tamil Nadu, Andhra Pradesh, Kerala and Karnataka).

The HIV status was confirmed by a dually reactive ELISA test.

All subjects satisfied the medical eligibility for initiation of antiretroviral therapy

(WHO stage III /IV or WHO stage I/II with CD4 counts less than 200 cells/µL)

The subjects had to be **ART naive** (defined as having received less than 4 weeks of ART prior to enrolment) and had to be initiated on HAART after March 1, 2004.

Exclusion criteria:

1. Pregnancy
2. Lactation
3. Age less than 12 years

Subject enrolment:

ART-naïve HIV infected adults eligible for and initiated on HAART after March 1, 2004 were included in the study. All patients satisfying the inclusion criteria were subjected to a standardized clinical interview at the time of enrolment. Baseline anthropometric data including weight, height, body mass index (BMI) were recorded. A blood sample was drawn for baseline complete blood counts (CBC), biochemical tests (blood glucose, liver and renal function tests), CD4 counts and plasma viral load (if feasible).

All these details were recorded in a standardized proforma (see Appendix).

All subjects had a detailed symptom directed clinical evaluation to rule out any active opportunistic infections prior to initiation of HAART.

Follow up clinical assessments were done every 3 months. Clinical evaluation included symptomatology and detailed physical examination. Cohort surveillance was mainly passive. Patients had open access to the study clinic and were encouraged to attend whenever ill. Each episode of illness was investigated and managed according to established protocols.

The review of patients for the study ceased on May 31, 2006

Study outcomes:

Primary outcome was the incidence of failure of the initial HAART regimen in the cohort. "Failure" was defined as any event which necessitated a change in or discontinuation of the initial HAART regimen. This included

1. **Death** from any cause.
2. **Clinical failure**: Clinical failure was defined as the diagnosis of a new AIDS-defining illness three months (to exclude IRIS) after the initiation of HAART.
3. **Immunological failure**: Immunological failure was defined as a decline in CD4 cell counts below baseline values or failure of CD4 cell counts to increase above baseline values six months after initiation of HAART. CD4 cell counts were determined by immunophenotyping (flow cytometry or GUAVA).
4. **Virological failure**: Virological failure was defined as either lack of viral suppression to below lower limit of quantification after six months of initiation of HAART or rebound increase in the viral load above the limit of quantification during the study period after an initial suppression. Plasma HIV viral load was determined using 'Real Time RT-PCR' (reverse transcriptase- polymerase chain reaction). The lower limit of quantification using the above technique was HIV RNA less than 53copies/mL.
5. **Non-adherence to therapy**: Non-adherence was defined as ingestion of less than 90 % of the prescribed doses. Adherence was assessed by patient self reporting and confirmed by pill count. Patients who never returned for follow-up after initiation of HAART were also considered to be non-adherent.

6. **Serious ADR**: defined as drug toxicities necessitating a regimen change. These have been discussed in detail below.

Secondary outcome was the incidence of severe adverse drug reactions (ADR). The main ADR necessitating regimen change includes NNRTI induced hypersensitivity reactions (severe rash and hepatitis) and NRTI induced complications like severe anemia, lactic acidosis and peripheral neuropathy.

a) Severe Drug Rash:

Occurrence of serious cutaneous manifestations like Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) or the syndrome of drug rash, eosinophilia and systemic symptoms (DRESS syndrome) in patients receiving HAART.

b) Hepatitis:

Hepatitis was defined as an elevation in serum transaminases (AST/ALT) to more than five times the upper limit of normal with or without symptoms after initiation of therapy.

c) Severe anemia:

Bone marrow suppression manifested by hemoglobin less than 8 g/dL, total leucocyte count less than 4000 cells/µL and platelet count less than 100,000/µL after initiation of therapy.

d) Symptomatic hyperlactatemia:

Patients on antiretroviral therapy with

1. Symptoms (which include fatigue, malaise, weight loss, anorexia, nausea, vomiting, dyspnea)

2. Metabolic acidosis (arterial pH less than 7.30 or bicarbonate less than 20 mmol/L) with increased anion gap (more than 20 mmol/L)

3. Elevated venous lactate concentration (>2 mmol/L, sample collected in a standardized manner**)

The following are the standard America and the Adult AIDS Clinical Trials Group (AACTG**) guidelines for specimen collection to determine venous lactate levels:

a) Have subject sit, relaxed for 5 minutes prior to venipuncture
b) Instruct subject to not clench the fist before or during the procedure and to relax the hand as much as possible
c) If possible, do not use a tourniquet. If a tourniquet is necessary, then apply tourniquet lightly and draw lactate first before the other samples with the tourniquet still in place
d) Collect the blood in a chilled gray-top (sodium fluoride-potassium oxalate) tube
e) Place the specimen immediately on ice and send to the laboratory for immediate processing, preferably within 30 minutes of collection.

4. Other causes of lactic acidosis like pancreatitis, dehydration, septicemia and acute hepatic failure need to be ruled out before confirming diagnosis of lactic acidosis.

e) Symptomatic peripheral neuropathy:

Peripheral neuropathy was ascertained based on signs and symptoms and could include sensory symptoms like tingling, numbness, loss of any sensory modality with or without motor deficits after initiation of ART. Symptomatic (intolerable sensory symptoms or

motor signs reported by the patient) peripheral neuropathy requires an interruption in treatment.

Statistical analysis:

Data entry was done using the Statistical Package for the Social Sciences (**SPSS)** software package (version **11)**. Descriptive statistics were calculated using SPSS software. Chi-square test was used for comparison of categorical variables. Odds ratio (OR) and confidence intervals (CI) were calculated and a 'p' value less than 0.05 was considered statistically significant. All reported p values are two-sided.

Univariate logistic regression models were constructed with "failure of HAART" as the dependent variable to determine the predictors of failure .

Variables with $p < 0.15$ in the univariate model were entered in the multivariate model.

Baseline parameters considered as possible predictors of the final outcome were age, sex, WHO clinical stage of illness, baseline CD4 cell counts, regimen used etc.

R E S U L T S

Baseline characteristics:

Between March 1, 2004 and May 31, 2006 (27 months), a total of 230 consecutive ART naive patients were enrolled into the study and followed up for a median period of 48 weeks.

The baseline characteristics of the patients are as listed below:

The study population mainly comprised of males (74.8%). The median age of the study population was 37 years (IQR, 34-44, mean (± S.D), 38.9 (± 8.4) years).

Table 1: Age category

Age (in years)	Number (%)
21-30	37 (16.1)
31-40	118 (51.3)
41-50	54 (23.5)
51-60	18 (7.8)
61-70	3 (1.3)
Total	230 (100)

The mode of acquisition of HIV infection was heterosexual transmission in the majority (98.7%). Two patients had transfusion transmitted HIV infection and one acquired infection through homosexual contact.

Majority of the patients had advanced stages of HIV infection, belonging to either WHO clinical stage III or IV (70.4 %). The distribution was as follows:

Table 2: WHO clinical stage of illness

WHO stage	Number (%)
WHO stage 1	8 (3.5)
WHO stage 2	60 (26.5)
WHO stage 3	104 (45.2)
WHO stage 4	58 (25.2)
Total	230 (100)

The median hemoglobin prior to initiation of HAART was 11.75 g/dL (IQR, 10.25-13).

The median serum creatinine prior to initiation of HAART was 0.9 mg/dL (IQR, 0.8 – 1.1, mean (± S.D), 0.94 (± 0.18) mg/dL)

Baseline CD4 cell counts:

Median CD4 cell counts prior to initiation of HAART: 127.72 cells/µL

Inter-quartile range: 57 – 189.75 cells/µL

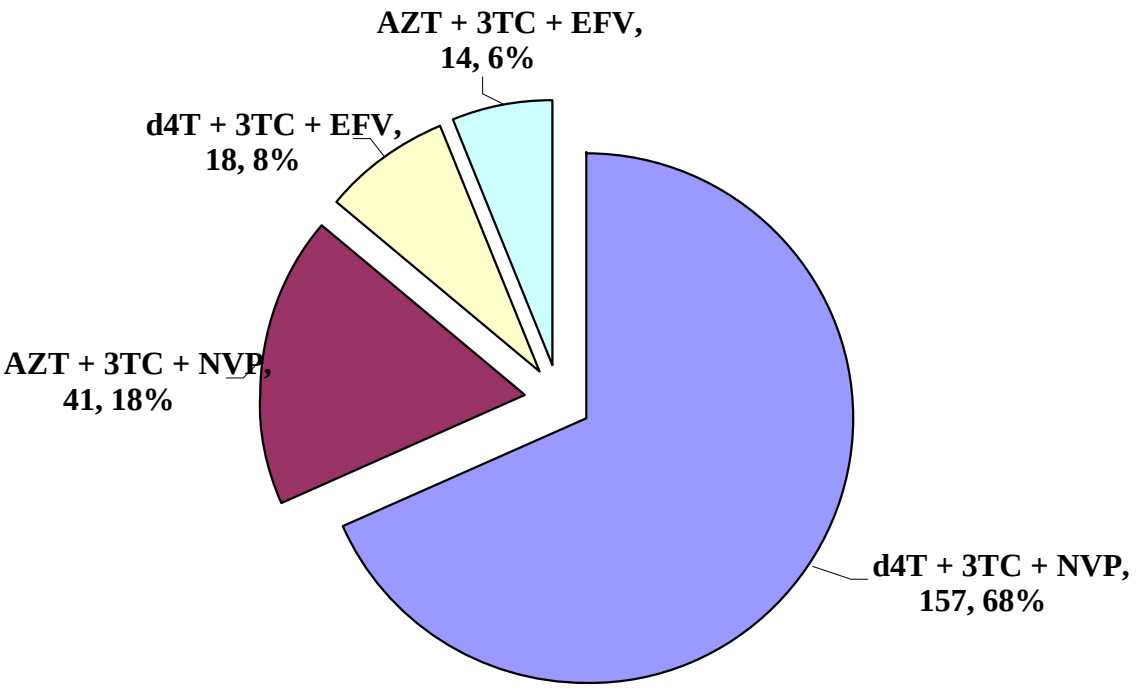
Mean CD4 cell counts prior to initiation of HAART: 112.5 (± 81.06) cells/µL.

Table 3: Distribution of individuals based on CD 4 counts

CD 4 category	Number (%)
Missing	*30*
< 50	42 (21)
50 - 200	113 (56.5)
> 200	45 (22.5)
Total	**200 (100)**

The absolute lymphocyte count was less than 1200 cells/µL in 58.1% of the patients.

Figure 1: HAART Regimen Used



d4T based regimen was used in 76% of the patients.

NVP was the NNRTI in 86% of the patients.

Twenty six (11.3 %) of the 230 patients also received concomitant anti-tuberculous therapy.

Concurrent trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis was being used in 99.6 % of patients. One patient was allergic to the above and received dapsone for prophylaxis.

Follow up:

The median duration of follow up was 48 weeks (IQR, 16 - 52 weeks, mean (±S.D), 39 (+/-24.2) weeks).

Failure of initial HAART regimen:

During the median duration of follow up of 48 weeks, 91 patients (39.6%) of patients experienced failure of their initial HAART regimen and had to either discontinue or change their initial HAART regimen.

Table 5: Causes of failure of initial HAART regimen

Event	Frequency (%)	Incidence rate (per 100 person-years)
Drug toxicity	62 (68.1)	35.9
Non-adherence	19 (20.9)	11
Clinical failure	7 (7.7)	4.1
Deaths **	3 (3.3)	2.4
Total	**91 (100)**	

The median time to regimen failure was 12 weeks.

** Eight patients died during the follow-up (incidence rate of 4.6/100 person-years). Three of them were attributed to clinical failure, two were due to ADR and three were due to unrelated causes.

Figure 2: <u>Kaplan – Meir survival analysis curve plotting the proportion of patients still continuing their initial regimen.</u>

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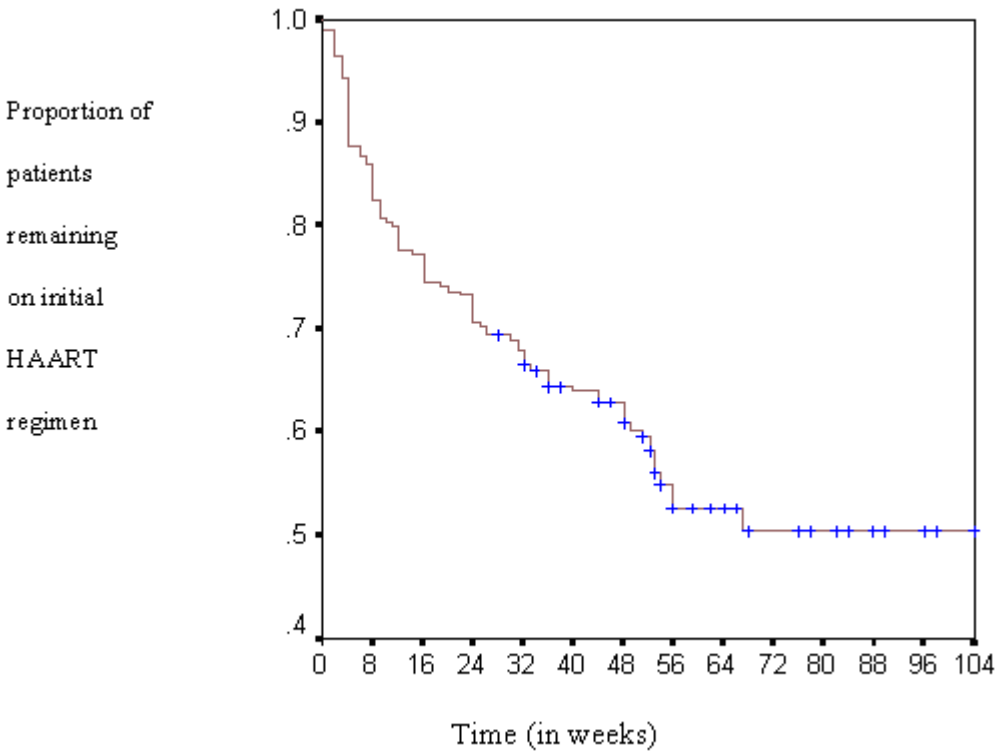

Around 60.4% of the patients are on their initial HAART regimen at the end of the median follow up period of 48 weeks as shown in the survival analysis curve. There is a steep fall during the initial phase indicating that the chance of failure is maximum in the first few weeks on initiation of HAART. The reasons for early HAART failure included loss to follow up, occurrence of an early ADR like anemia and drug rash.

Reasons for failure of initial HAART regimen:

1. Deaths:

There were a total of 8 deaths (3.5%) in the study cohort. The incidence rate was 4.6/100 person-years. Five of them were due to failure of HAART and three of them were due to unrelated causes. Two patients died of ADR- one patient each developed TEN and lactic acidosis. Three patients died due to disease progression while on HAART (clinical failure).

2. Adverse Drug Reactions:

Serious ADR occurred in 62 patients (27%) and was the commonest cause of failure of the initial HAART regimen in the study cohort

The incidence rate for ADR was 35.9/100 person-years.

The incidence and profile of individual drug toxicities is illustrated in detail in the subsequent sections.

3. Non-adherence:

Nineteen patients (8.3%) had to discontinue their regimen due to non-adherence. As mentioned before adherence rates were calculated using patient self report and pill count and patients with adherence rates persistently below 90 % were termed non-adherent. The patients who did not follow up after initiation of HAART have also been included in this analysis.

The incidence rate for non-adherence was 11/100 person-years.

4. Clinical Failure:

Seven patients (3%) developed newer AIDS-defining illnesses during the follow-up period, an incidence rate of 4.1/100 person years. The major illnesses were disseminated tuberculosis which occurred in all seven patients and cytomegalovirus infection in one patient. Four of these patients also had oropharyngeal candidiasis. Three patients eventually succumbed to these illnesses.

Immune Reconstitution Inflammatory Syndromes:

Overall, eleven patients (4.8%) developed IRIS. The incidence rate for IRIS was 6.4/100 person-years. Ten patients developed IRIS with *Mycobacterium tuberculosis*. These immune reconstitution syndromes occurred within the first three months of initiation of HAART and these patients required a change from a NVP- based regimen to an EFV-based regimen to avoid potential drug interactions between NVP and Rifampicin. One patient developed immune restoration illness with *Cryptococcus neoformans;* however he continued the initial HAART regimen.

Determinants of failure of initial HAART regimen:

A univariate logistic regression analysis showed the following parameters to be predictors of failure of initial HAART regimen (see table):

1. Advanced HIV infection (WHO clinical stage III, IV) [OR 1.59, 95% CI (1.38-1.88)].
2. BMI > 25 [OR 1.56, 95% CI (1.18-2.06)].

3. Concurrent smoking [OR 2.16, 95% CI (1.52-3.06)].

4. AST levels > 40 U/L [OR 2.26, 95% CI (1.47-3.47)]

5. ALT levels > 40 U/L [OR 4.07, 95% CI (2.36-6.99)]

6. Duration of illness before initiation of HAART more than 3 months [OR 1.22, 95% CI (1.04-1.44)].

Age, sex, HIV transmission category, CD4 cell counts and individual regimens were not associated with the failure of initial HAART.

When the parameters with P value < 0.15 were entered in the multivariate logistic regression analysis, advanced HIV infection, BMI more than 25, baseline elevated alanine aminotransferases (ALT) and concurrent smoking remained predictive for HAART failure.

Table 6: Predictors for failure of initial HAART regimen (univariate)

Parameter	Odds ratio	95% CI	P value
Female sex	1.11	0.71-1.74	0.636
Advanced HIV (WHO clinical stage III, IV)	1.59	1.38-1.88	**<0.001**
BMI > 25	1.56	1.18-2.06	**<0.001**
Smoking	2.16	1.52-3.06	**<0.001**
Duration of illness >3 months	1.22	1.04-1.44	**0.017**
CD4 < 200 /µL	1.02	0.88-1.19	0.791
ALC < 1200 /µL	1.21	0.97-1.50	0.093
Diabetes mellitus	0.62	0.22-1.74	0.359
Creatinine clearance < 50 mL/min	1.10	0.96-1.04	0.938
AST > 40 U/L	2.26	1.47-3.47	**0.009**
ALT > 40 U/L	4.07	2.36-6.99	**<0.001**
TMP-SMX prophylaxis	1.01	0.99-1.02	0.393
Concurrent ATT	1.18	0.57-2.43	0.663
AZT- based regimen	1.59	0.91-2.72	0.100

Severe adverse drug reactions:

Severe ADR was the commonest cause of discontinuation of initial HAART in our study population (62 patients, incidence rate of 35.9/100 person-years).

Table 7: Incidence of ADR

ADR	Frequency (Cumulative incidence)	Incidence rate (per 100 person-years)
Symptomatic hyperlactatemia	20 (8.7%)	11.6
Severe anemia	16 (7.0%)	9.3
Peripheral neuropathy	12 (5.2%)	7.0
Severe drug rash	9 (3.9%)	5.2
Hepatitis	3 (1.3 %)	1.7
Others (pancreatitis)	2 (0.9 %)	1.1
Total	**62 (27%)**	**35.9**

The major determinants for occurrence of an ADR were:

1. Advanced HIV infection [OR 1.39, 95% CI (1.21-1.61)]

2. Smoking [OR 1.51, 95% CI (1.08-2.11)]

3. BMI > 25 [OR 1.68, 95% CI (1.29-2.18)]

4. AST > 40 U/L [OR 1.93, 95% CI (1.29-2.89)]

5. ALT > 40 U/L [OR 2.48, 95% CI (1.6-3.49)]

The other potential predictors for development of a severe adverse drug reaction are given in the table.

Table 8: Predictors for development of severe ADR

Parameter	OR	95% C. I	P value
Advanced HIV infection (WHO clinical stage III,IV)	1.39	1.21-1.61	**< 0.001**
BMI > 25	1.68	1.29-2.18	**<0.001**
smoking	1.51	1.08-2.11	**0.02**
Female sex	1.19	0.74-1.90	0.487
CD4>200 cells/µL	1.13	0.65-1.95	0.677
ALC<1200cells/µL	0.97	0.76-1.25	0.811
AST > 40 U/L	1.93	1.29-2.89	**0.002**
ALT > 40 U/L	2.48	1.60-3.49	**0.001**
TMP-SMX prophylaxis	1.01	0.93-1.02	0.538
Concurrent ATT	0.48	0.17-1.34	0.14
AZT-based regimen	1.58	0.89-2.80	0.119
Creatinine Clearance < 70mL/min	0.99	0.57-1.70	0.964

Individual drug toxicities:

Severe Drug rash:

The incidence of severe drug rash (SJS or TEN) was 5.2/100 person-years.

Nine patients developed severe drug rash. NVP was the etiology in eight of them and one patient developed drug rash to AZT. The median time to discontinuation of therapy due to severe drug rash was 2 weeks [range 2-6 weeks].

All patients received NVP in a once daily lead - in- dose for 2 weeks before escalation to twice daily dosage.

The offending drug was discontinued in all these patients. One patient died of TEN syndrome due to NVP.

Severe anemia:

The incidence of drug induced anemia was 9.3/100 person-years.

The median time to detection of anemia was 8 weeks [range 3-36 weeks].

AZT was the offending drug in all the cases and discontinued. A d4T-based regimen was used instead.

Symptomatic hyperlactatemia:

The incidence of symptomatic hyperlactatemia was 11.6/100 person-years.

Hyperlactatemia occurred only in patients on d4T- based regimens. Median time to development of symptomatic hyperlactatemia was 42 weeks [range 24-67 weeks].

The mean HCO3 and anion gap levels for these patients were 15 (± 5.3) mmol/L and 22.5 (± 6.4) mmol/L respectively. The mean venous lactate was 3.7 mmol/L. All these patients received a drug holiday and were later started on an AZT- based regimen which they tolerated well. One patient died due to severe lactic acidosis.

Peripheral neuropathy:

Incidence of peripheral neuropathy was 7/100 person-years.

Median time to development of the same was 32 weeks [Range 20-56 weeks].

Peripheral neuropathy was more likely to develop with a d4T-based regimen.

DISCUSSION

This study reveals a **very high rate of failure** of the initial HAART regimen in a cohort of south Indian adults with advanced HIV infection. Majority (70.4%) of the patients had advanced clinical stages of HIV infection (WHO stage III/IV) or CD4 cell counts less than 200cells/µL (78.5%). The male preponderance implies that males have a better access to therapy rather than the epidemiological profile of HIV infection in our setup. A very high proportion of the patients were on d4T-based regimens (76.1%) and 86.1% had NVP as the NNRTI. At the end of the median follow-up period of 48 weeks, 39.6% of patients had either discontinued or changed their initial HAART regimen. These regimen failure rates are very high compared to references from published literature. In the study conducted at YRG CARE centre, Kumarasamy et al had described treatment modification rates of 20%, the main reasons being adverse events, cost and treatment failure.**(5)** In a US-based ART naïve cohort, Yuan et al had described treatment discontinuation rates of 39.3% over a median follow up of 211 days.**(26)**

The median time of follow up in our study was 48 weeks. It is important to realize that this time of 48 weeks is a **relatively short time** in view of the need for lifelong therapy. The incidence of regimen failure was higher in the first few weeks of initiation of HAART as shown in the Kaplan –Meier survival analysis curve earlier. The median time to regimen failure was 12 weeks. The reasons for HAART regimen failure during the initial phases of therapy were non-adherence/loss to follow-up and early ADR like anemia and severe drug rash.

Drug related toxicities are a frequent cause of modification of the initial HAART regimen. In our study, 27 % of the subjects developed severe ADR requiring either a change or discontinuation in the initial HAART regimen. The major ADR in our cohort were symptomatic hyperlactatemia (8.7%), severe anemia (7%) and peripheral neuropathy (5.2%). All these ADR are attributable to the **thymidine analogue** NRTI used in the backbone- either d4T or AZT. The mitochondrial toxicities of NRTIs appeared later during the course of therapy. The median duration to development of hyperlactatemia was 42 weeks and peripheral neuropathy was 32 weeks. An intriguing observation was that some patients who had discontinued the HAART regimen due to lactic acidosis actually reported symptoms suggestive of peripheral neuropathy during the earlier follow-up visits. The patients receiving NVP were at a higher risk of developing severe drug rash or hepatitis.

The major predictors for development of an ADR were advanced stages of HIV infection, obesity, elevated transaminases and concurrent smoking. Our findings are consistent with the recent publication by Kumarasamy et al in which ADR was a major cause of treatment modification in 64% of their study population. The best solution to increase the tolerability of HAART in view of the high incidence of thymidine analogue NRTI related ADR would be to start eligible PLHA on **non-thymidine analogue** NRTI like **Tenofovir (TDF)** which have **favorable efficacy and safety profiles**.

Another major observation was the **low mortality** (4.6/100 person-years) **and disease progression rates** (4.1/100 person-years). There were total of 8 deaths and 7 patients developed new AIDS-defining illnesses while on HAART. These findings confirm the **effectiveness of generic HAART** in substantially reducing the morbidity and mortality even among patients with advanced HIV infection.

This study also reiterates the fact that by increasing the tolerability of HAART, one can achieve significant reductions in regimen failure rates.

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The **definition of "failure**" of HAART regimen used in our study is a very **practical** one which incorporates regimen safety, tolerability and convenience, in addition to potency. The main causes of failure of a HAART regimen based on previous studies and adopted by the AIDS control trial group (ACTG) have been drug toxicities, clinical, virological or immunological failure and non-adherence to therapy. Serial monitoring of plasma viral loads and CD4 counts while on therapy might not be feasible in developing country with most centers having limited resources. Hence the decision to change a regimen is most often taken on the basis of serial clinical assessments, drug toxicities, development of newer AIDS-defining illnesses while on HAART etc.

Eleven patients were diagnosed to have IRIS. These patients presented with opportunistic infections usually within the first three months of initiation of antiretroviral therapy. These do not represent failure of HAART. Majority of our patients had *Mycobacterium tuberculosis* presenting as immune reconstitution syndromes requiring a change from

NVP to an EFV based regimen to avoid drug interactions between RIF and NVP. The phenomenon of immune reconstitution is believed to occur due to initial rapid increases in CD4 counts due to redistribution of trapped memory T cells from the lymph nodes to peripheral blood, followed by a slower repopulation of newly produced naive T cells.

Our cohort had relatively **low non-adherence rates** (11/100 person-years). The rate is lower when compared to previous studies which have documented rates as high as 13.4%.**(26)** This is hugely attributable to the meticulous efforts by the support staff concentrating on aspects of patient education. Optimizing adherence is truly the cornerstone of a successful response to a HAART regimen.

To summarize:

1. The incidence of death and disease progression was low in this cohort, indicating effectiveness of HAART even in patients with advanced HIV infection.

2. The major cause of HAART failure was ADR, mainly to the thymidine analogue NRTI backbone components- d4T and AZT. Hence there is a need for selecting regimens with better safety profiles like Tenofovir based regimens to enhance the tolerability and reduce the incidence of HAART failure.

3. By recruiting full term personnel emphasizing on continuous patient education and limiting substance abuse through detailed psychosocial evaluation one can reduce the incidence of non-adherence.

4. Advanced HIV illness is associated with a higher risk of HAART failure; hence there is a case for initiation of HAART earlier in the course of illness, though concerns about

the tolerability might always discourage initiation of HAART in relatively asymptomatic patients.

The major **limitations** in our study include:

1. The median duration of follow-up of 48 weeks actually represents a very short time frame considering the chronicity of the illness and the need for lifelong treatment.
2. According to existing guidelines, there should be periodic monitoring of CD4 cell counts and plasma viral loads during the course of therapy to ensure that the regimen offers maximum virological suppression. Only one patient in our study cohort could afford serial monitoring of CD4 counts and plasma viral loads.

Clearly, a lot of improvement is still needed in the field of antiretroviral therapy.

1. To reduce the incidence of treatment failure, ART should cause lesser toxicity and adherence should become much easier.
2. Risk factors other than patient reported reasons might contribute to treatment discontinuation. There is a need for identifying these risk factors and simplifying treatment regimens for maximizing effectiveness of ART.
3. Cost effective monitoring tools need to be devised in developing countries with limited resources.

CONCLUSIONS

1. Two hundred and thirty consecutive ART naïve HIV infected individuals initiated on HAART after March 1, 2004 were followed up for a median period of 48 weeks.
2. Failure of the initial HAART regimen occurred in 91 (39.6%) of these patients.
3. HAART regimen failure was mainly due to ADR (68.1%), non-adherence (20.1%) and clinical failure (7.7%). The commonest ADR were symptomatic hyperlactatemia (8.7%), severe anemia (7%) and peripheral neuropathy (5.2%) which was either due to the d4T/AZT component of the HAART regimen.
4. The main predictors for HAART regimen failure were advanced HIV infection, obesity, concurrent smoking, elevated transaminases and duration of illness before initiation of HAART more than 3 months.
5. The incidence of mortality in our study cohort was low (4.6/100 person-years)
6. The incidence of newer AIDS-defining illnesses signifying disease progression was also low (4.1/100 person-years) among this cohort with advanced HIV infection.
7. The major determinants for occurrence of an ADR were advanced HIV infection, smoking, obesity and elevated transaminases.

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ABSTRACT

Title: Incidence and determinants of failure of the initial highly active antiretroviral therapy (HAART) regimen in a cohort of ART naïve HIV infected south Indian adults.

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Objectives of the study:

To determine the incidence and predictors of failure of the initial HAART regimen in a cohort of ART-naïve, HIV-infected south Indian adults

Methods:

A cohort of ART-naïve HIV-infected south Indian adults who were initiated on HAART (as per WHO and NACO guidelines) after March 1, 2004 were prospectively followed up. “Failure” was defined as any event requiring either discontinuation or change in the initial HAART regimen. This included virological, immunological or clinical failure, serious ADR, non-adherence and death. A logistic regression analysis was performed to determine the factors associated with HAART failure.

Results:

Two hundred and thirty subjects were enrolled during the 27 months from March 1, 2004 to May 31, 2006. The median age was 37 years (IQR, 34-44) and 74.8% of the subjects were males. Majority (70.4%) had advanced HIV infection (WHO clinical stage III/IV) and 79% had CD4 counts below 200 cells/µL. Stavudine-based regimen was used in 76% and 86% were on a NVP-based regimen. During the median follow-up of 48 weeks, 91 (39.6%) patients experienced failure. The main reasons for failure were ADR (68.1%), non-adherence (20.9%) and clinical failure (7.7%). The most common ADR were attributable to the thymidine analogue NRTIs - d4T induced symptomatic hyperlactatemia (8.7%), peripheral neuropathy (5.2%), and AZT induced anemia (7%). The mortality (4.6/100 person-years) and disease progression rates (4.1/100 person-years) were low. Advanced HIV infection (OR 1.59), smoking (OR 2.16), BMI > 25 kg/sq.m (OR 1.56), deranged liver enzymes (ALT > 40U/L - OR 2.25, AST > 40U/L - OR 4.07) and longer duration of illness (OR 1.224) were associated with HAART failure.

Conclusion:

HAART regimens used in this study, though effective in decreasing the rates of disease progression and death, were associated with high rates of ADR, particularly those attributable to thymidine analogue NRTI. **Improving access, earlier initiation, careful screening at baseline and better tolerated drug regimens could potentially improve the outcome of these patients.**

Appendix I

Proforma

1. Name

2. Age

3. Sex

4. Hospital No.

5. Address

Phone No.

6. smoker/nonsmoker

7. Occupation

8. Marital status: never married /currently married/separated/widowed

9. Education: Nil/primary/secondary/high school/college

10. Date of diagnosis of HIV infection-

Test by which diagnosis made- ELISA/Western Blot

11. Opportunistic infections prior to HAART:

Date	Opportunistic infection	treatment

12. WHO clinical stage of infection (at initiation of HAART): I /II /III /IV

13. Diseases prior to initiation of ART: HTN/ DM/ Dyslipidemia/ others

14. VDRL: Nonreactive/reactive

15. HBsAg: positive/negative

16. HCV ab :positive/negative

17. Body weight:

Height:

18. BMI:

19. Relevant physical findings:

20. Investigations: 1 .Hb

2. TC/DC ALC

3. Platelets

4. AC/PC

5. Lipid profile

6. LFT

7. Serum creatinine

8. CXR

9. Urine protein

21. CD4 counts (prior to HAART)

22. HIV viral load

23. HAART regimen:

Regimen 1-Stavudine-30+lamivudine+nevirapine

Regimen 2-stavudine-40+lamivudine+nevirapine

Regimen 3-Zidovudine+lamivudine+nevirapine

Regimen 4-Zidovudine+lamivudine+efavirenz

Regimen 5-stavudine-30+lamivudine+efavirenz

Regimen 6-stavudine-40+lamivudine+efavirenz

Any others-to specify

To specify whether any change in regimen at any time:

24. Whether on: 1.ATT 2.Bactrim 3.MVT

25. Drug toxicity:

a. Dermatological: skin rash [ ],oral ulcers [ ]

b.GI disturbances: nausea [ ],vomiting [ ],hepatitis [ ],pancreatitis [ ]

c. Bone marrow toxicity:

d. Metabolic:glucose intolerance [ ],dyslipidemia [ ],lipodystrophy [ ],lactic acidosis [ ]

e. Neurological:peripheral neuropathy [ ],myopathy [ ]

f. Renal stones [ ]

g.others: specify

25. Whether any OI on HAART (IRIS)-specify also the mode of management

26. Follow-up

Date	weight	Adherence%	toxicity	CD4	PVL	New events

27. At end of study:

1. Weight
2. Bodymass index
3. Midarm circumference
4. Hb
5. Blood sugars
6. Lipid profile
7. ALC
8. CD4 counts

Consent form

Title of study: Incidence and determinants of failure of initial HAART regimen in a cohort of ART naïve HIV infected South Indian adults.

Institution: Department of Medicine and Infectious diseases.

Purpose of study : A descriptive study to determine the incidence and determinants of treatment failure in a cohort of ART naïve HIV infected South Indian adults.

Declaration by the patient

After initiation of ART, I agree to regularly follow up in the Infectious Disease OPD as per my doctors advice and also report any major events as explained by my doctors . I also understand that I have an open access to the study clinic and can report any time to either the department or emergency services if the need arises.

I also understand that all my details and records obtained for the purpose of the study will need to be available to the doctor conducting the study , but will remain strictly confidential at all times. My identity will not be otherwise revealed.

I have read the above information before signing the consent form.

Place:

Date: Name and signature

Signature of principal investigator

Appendix II:

GLOSSARY TO MASTER CHART

1. Name

2. Hospital number

3. Age in years

4. Sex (1 – female, 2 - male)

5. Transmission: Mode of transmission (1-heterosexual, 2-homosexual, 3-IV drug abuse, 4-transfusion related)

6. Stage: WHO stage of HIV illness (1-Stage 1, 2-Stage II, 3- Stage III, 4-Stage IV)

7. Duration of illness prior to initiation of HAART in weeks.

8. Co-morbidities: (0-none, 1-Diabetes mellitus, 2-Hepatitis B infection, 3-Hepatitis C infection, 4-syphilis, 5-others)

9. Body weight (in kg) at time of initiation of HAART.

10. Height in cms.

11. CD 4 lymphocyte cell counts per cubic mm.

12. ALC: Absolute lymphocyte counts.

13. Hemoglobin in g/dL.

14. Serum creatinine in mg/dL..

15. AST:aspartate aminotransferase (1–normal < 40 U/L, 2–elevated >40 U/L)

16. ALT: alanine aminotransferase (1–normal < 40 U/L, 2–elevated >40U/L)

17. ART regimen used: (1-d4T + 3TC + NVP

2-AZT + 3TC + NVP

3-d4T + 3TC + EFV

4- AZT + 3TC + EFV)

18. Concurrrent use of TMP-SMX prophylaxis: (1-yes, 2-no)

19. Concurrent antituberculous therapy (1-yes, 2-no)

20. End point: treatment failure (1 –yes, 2-no)

21. Reason for treatment failure/regimen discontinuation: (0- still on HAART

1- drug toxicity

2- clinical failure

3- non-adherence

4- death

5- others)

22. Drug toxicity: (0- none,

1- Drug rash,

2- Hepatitis

3- Anemia

4- Hyperlactatemia

5- Peripheral neuropathy

6- Others

23. Smoking: (1-yes, 2-no)

24. Death: (1 –alive, 2 – death)

25. Total follow-up in weeks.

Appendix III

Revised WHO Clinical Staging of HIV/AIDS for Adults and Adolescents

Primary HIV infection

Asymptomatic
Acute retroviral syndrome

Clinical stage 1

Asymptomatic
Persistent generalized lymphadenopathy

Clinical stage 2

Moderate and unexplained weight loss (<10% of presumed or measured body weight)
Recurrent respiratory tract infections (such as sinusitis, bronchitis, otitis media, pharyngitis)
Herpes zoster
Recurrent oral ulcerations
Papular pruritic eruptions
Angular cheilitis
Seborrhoeic dermatitis
Fungal finger nail infections

Clinical stage 3

Conditions where a presumptive diagnosis can be made on the basis of clinical signs or simple investigations
Unexplained chronic diarrhoea for longer than one month
Unexplained persistent fever (intermittent or constant for longer than one month)
Severe weight loss (>10% of presumed or measured body weight)
Oral candidiasis
Oral hairy leukoplakia
Pulmonary tuberculosis (TB) diagnosed in last two years
Severe presumed bacterial infections (e.g. pneumonia, empyema, meningitis, bacteraemia, pyomyositis, bone or joint infection)
Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis

Conditions where confirmatory diagnostic testing is necessary
Unexplained anaemia (< 80 g/l), and or neutropenia (<500/µl) and or thrombocytopenia (<50 000/ µl) for more than one month

Clinical stage 4

Conditions where a presumptive diagnosis can be made on the basis of clinical signs or simple investigations
HIV wasting syndrome
Pneumocystis pneumonia
Recurrent severe or radiological bacterial pneumonia
Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration)
Oesophageal candidiasis
Extrapulmonary Tuberculosis
Kaposi's sarcoma
Central nervous system toxoplasmosis
HIV encephalopathy

Conditions where confirmatory diagnostic testing is necessary
Extrapulmonary cryptococcosis including meningitis
Disseminated non-tuberculous mycobacteria infection
Progressive multifocal leukoencephalopathy
Candida of trachea, bronchi or lungs
Cryptosporidiosis
Isosporiasis
Visceral herpes simplex infection
Cytomegalovirus (CMV) infection (retinitis or of an organ other than liver, spleen or lymph nodes)
Any disseminated mycosis (e.g. histoplasmosis, coccidiomycosis, penicilliosis)
Recurrent non-typhoidal salmonella septicaemia
Lymphoma (cerebral or B cell non-Hodgkin)
Invasive cervical carcinoma
Visceral leishmaniasis

NAME	H.no.	age	sex	ransmissio	stg	duration	comorbid	weight	height	cd4	ALC	hb	crt	AST	ALT	regimen	bactrim
abdul kare	254502c	44	2	1	4	156	0	49	166	97	1316	11	1	2	2	1	1
abdul suba	359424c	45	2	1	3	36	0	64	162	124	1700	13	1	2	2	1	1
adinarayan	033765c	40	2	1	3	140	0	44	168	223	2800	12	1	1	1	1	1
abooty	474084c	50	2	1	4	676	0	60	175	112	1456	10	1	1	2	4	1
ahmed jam	138827c	38	2	1	4	148	0	50	171	13	832	9.4	0.9	2	1	1	1
alamelu	536611c	26	1	1	3	4	0	45	158	.	900	9.4	1	.	.	1	1
amar	347336c	33	2	1	3	16	0	43	160	148	390	9.8	0.9	1	1	1	1
andiappan	535676c	46	2	1	3	4	0	55	169	74	462	12	1	1	1	1	1
annamalai	680996c	27	2	1	2	16	0	46	163	159	1224	15	0.8	1	1	1	1
anthony.x	424625c	49	2	1	2	12	0	56	168	162	978	12	1	1	1	1	1
annadurai	475449c	46	2	1	3	126	0	59	166	112	2340	16	2	1	2	1	1
arputha raj	841617b	41	2	1	3	156	0	54	162	43	925	8.3	1	1	1	1	1
arockiados	658904c	57	2	1	3	8	0	47	163	82	1182	10	0.7	2	2	1	1
arul.a	411892c	34	2	1	3	76	0	50	170	107	1463	11	1	1	1	2	1
aruna	488816c	30	1	1	2	4	0	45	168	272	2400	12	0.7	1	1	1	1
ashokan	573090c	43	2	1	3	16	0	44	169	69	968	11	0.6	2	2	1	1
babu.k	558566c	36	2	1	1	48	0	58	173	185	2400	14	1	1	1	1	1
babu.m	544829c	40	2	1	1	32	0	56	165	210	1794	12	0.9	1	1	2	1
balaji.b	159036c	40	2	1	4	104	0	59	161	18	980	10	0.8	1	1	3	1
balasubran	527509c	54	2	1	4	24	0	66	164	20	636	11	1	2	2	3	1
chandrayu	423815c	33	2	1	3	48	0	60	174	64	.	7.5	1	2	1	1	1
baskaran.c	645584b	41	2	1	3	32	0	43	160	.	2870	13	1	1	1	1	1
baskaran.g	564232c	45	2	1	2	48	0	70	173	68	1196	12	0.9	1	1	1	1
baskar.v	719665c	40	2	1	3	12	2	73	171	302	1352	17	1	2	2	4	1
bhanumath	610885c	45	1	1	3	24	0	45	151	25	1632	8.6	0.8	2	1	2	1
bhujamma	491258c	50	1	1	1	8	0	58	155	303	3000	11	1	1	1	1	1
brinda.s	709012c	46	1	1	2	4	1	48	151	.	1836	12	0.7	2	2	4	1
caroline ma	627091c	37	1	1	3	56	0	46	150	219	1829	9.9	0.8	1	1	3	1
chabungar	696833c	35	2	1	3	810	3	61	164	205	1406	16	0.9	2	2	1	1
chakrapani	072199c	27	2	1	3	780	0	46	166	233	1750	12	0.9	1	1	2	1
challa lalith	665245c	31	1	1	2	2	0	43	154	191	2160	9.9	0.7	2	2	1	1
chandran.r	439747c	35	2	1	2	2	0	51	166	126	740	12	0.8	1	1	1	1
chandrada	391517c	30	2	1	4	48	0	56	164	149	1155	13	1	1	1	1	1
chandramo	518574c	50	2	1	3	16	0	42	167	.	1209	11	0.9	1	1	3	1
chandrasel	223757c	34	2	1	3	104	0	59	165	173	3150	12	1	1	1	1	1

chandrayu	423815c	34	2	1	2	48	0	62	169	64	1242	12	1	1	1	1	1
chella venk	665241c	37	2	1	2	4	0	65	172	50	1080	11	0.8	1	1	2	1
deva	861879b	52	2	1	2	260	0	69	175	327	1277	14	1	2	2	2	1
devaki	721009c	40	1	1	3	24	0	51	154	75	777	11	0.9	1	1	4	1
dhanalaksh	316605c	27	1	1	3	66	0	55	148	272	1320	14	0.8	2	2	1	1
dhananjaya	505930c	40	2	1	2	4	0	55	168	202	1750	12	0.9	1	1	1	1
dharmaling	646995c	36	2	1	2	8	2	70	174	100	672	12	0.7	2	2	3	1
duraimurug	347422c	40	2	1	3	48	0	59	164	237	1296	14	1	1	1	1	1
elumalai	677811c	36	2	1	2	4	0	50	160	84	1290	14	0.9	1	1	1	1
emmanuel	432912c	35	2	1	4	36	0	56	154	24	740	11	0.8	2	2	1	1
eshwara pr	514141c	32	2	1	3	104	0	60	168	200	1224	12	1	1	1	1	1
florence pr	310654c	34	1	1	2	104	2	46	150	133	976	10	0.9	1	1	1	1
ganapathy	179890c	39	2	1	2	52	0	83	170	237	3080	15	1	.	.	1	1
ganesan.r	043172c	39	2	1	3	208	0	51	160	69	384	11	1	1	1	2	1
ganesh kur	600287b	29	2	1	2	156	0	60	172	122	1144	17	1	1	1	1	1
gourishank	191007c	30	2	1	4	104	0	49	158	.	1980	12	0.9	1	1	1	1
govindan.s	580861b	46	2	1	4	208	1	64	160	45	1188	13	0.9	2	2	1	1
govindaraj	650718c	34	2	1	2	8	0	60	173	141	1924	13	0.8	.	.	1	1
govindasw	294987b	45	2	1	3	104	0	58	166	50	855	13	0.9	1	1	3	1
gunasekhr	545887c	38	2	1	3	24	0	65	160	50	868	13	0.9	1	2	1	1
haneefa t	434337c	40	2	1	3	12	0	69	171	128	720	7.8	1	1	1	3	1
hanumanth	633144c	55	2	1	3	24	0	64	172	118	1150	13	1	1	2	2	1
hari.v	563056c	34	2	1	3	8	4	67	168	186	1260	14	1	.	.	2	1
janaki r	714471c	46	1	1	3	4	0	46	154	30	1700	12	0.8	1	1	1	1
jayakrishna	400385c	47	2	1	3	.	1	71	170	209	1800	8.2	1	1	1	1	1
jayapal.r	805187b	44	2	1	2	208	0	75	168	157	2000	15	1	1	2	1	1
jayshree.s	461906c	25	1	1	1	8	0	.	.	229	1980	8.6	0.7	1	1	1	1
jeyachandr	600944c	56	2	1	4	104	0	35	169	.	316	9.8	0.9	1	2	1	1
jeyanthi	333356b	34	1	1	2	4	0	64	158	204	1400	14	0.8	1	1	2	1
johnson.o	737643c	39	2	1	4	8	0	40	158	10	852	11	1	2	2	1	1
juli.j	341422c	28	1	1	4	52	0	41	152	20	390	8.1	0.8	1	2	1	1
kala.m	161412b	40	1	1	4	520	4	56	150	111	1106	10	0.8	1	1	1	1
kanchana	743845c	31	1	1	3	2	0	38	148	17	1048	11	0.7	1	1	1	1
kaliappan.a	369114c	40	2	1	3	36	0	65	168	50	1080	13	0.8	1	2	1	1
kannan	426184c	32	2	1	3	16	0	66	170	222	.	.	.	1	1	1	1
karthikeyar	457963c	31	2	1	3	52	0	77	170	51	380	11	1	2	1	2	1

karupannal	453785c	54	2	1	4	16	1	56	171	59	1311	9.9	0.8	2	2	3	1
karunakara	023646c	42	2	1	2	52	1	65	173	184	2136	12	1	1	1	1	1
kavitha.g	178308c	30	1	1	1	156	0	56	158	294	1304	12	0.8	1	1	2	1
konda redc	609645c	47	2	1	3	8	0	55	172	102	860	9.2	1	2	1	4	1
koteeswari	591551c	29	1	1	3	16	0	54	156	.	1224	13	0.8	.	.	1	1
kousalya	268093c	56	1	1	4	84	0	56	158	90	1150	11	1	2	2	1	1
kumar.k	801815c	30	2	1	3	104	0	54	162	.	1100	12	0.7	2	2	4	1
kumaresar	369640c	35	2	1	3	98	0	45	168	.	860	12	1	2	2	1	1
kuttilakshm	591683c	38	1	1	2	84	0	53	157	121	1056	11	0.7	.	.	1	1
lakshmi	322007b	34	1	1	4	208	0	40	153	.	868	8.6	0.9	2	2	1	1
lakshmi de	646196c	28	1	1	3	4	0	38	148	201	1210	12	0.7	1	1	2	1
latha.d	928775b	35	1	1	3	208	0	47	149	102	555	.	0.7	1	1	1	1
madhesh.p	508789c	44	2	1	2	24	0	70	172	180	3000	15	0.9	1	1	2	1
madhubala	572866c	28	1	1	3	4	0	50	157	77	760	9.3	0.7	2	1	4	1
madhusud	964636b	29	2	1	3	452	0	45	161	32	1008	16	1	1	1	1	1
mageshwa	341317c	44	1	1	1	48	0	60	160	279	2310	13	1	1	1	1	1
maiyarasar	484716c	30	2	1	3	8	0	66	168	57	924	13	0.9	1	1	1	1
mahendrar	063994c	36	2	1	4	208	0	51	169	.	824	8.4	1	1	1	1	1
malliga.m	728067c	34	1	1	3	156	0	55	156	207	3000	14	0.8	2	2	2	1
manogarar	255399c	44	2	1	3	24	0	48	175	110	980	14	0.8	1	1	1	1
mani k	255248c	34	2	1	2	104	0	66	171	101	1043	14	0.8	1	1	1	1
manita	424999c	36	1	1	2	52	0	56	152	205	1258	11	0.7	1	1	1	1
mohan r	591480c	40	2	1	3	8	0	62	172	195	1530	13	1	1	1	2	1
manu idicu	649507c	35	2	1	4	8	0	54	167	53	600	14	0.9	1	1	2	1
mary susec	672441c	51	1	1	2	4	0	55	158	147	660	13	0.7	1	1	2	1
masilaman	725460c	38	2	1	2	52	0	60	171	.	1140	13	0.8	1	1	2	1
mohan bab	418920c	36	2	1	2	8	0	58	159	57	795	12	1	1	1	1	1
mohan rao	351749c	34	2	1	2	112	0	63	168	236	1280	15	1	1	1	2	1
munuswan	599627c	35	2	1	4	16	0	53	174	40	918	12	0.8	1	1	1	1
murali s	671659c	27	2	1	3	8	0	52	157	64	2094	12	1	1	1	1	1
murali moh	246549	32	2	1	3	98	0	56	166	146	2700	14	0.9	2	1	1	1
murugan.p	584365b	40	2	1	2	104	0	78	173	166	1600	15	1	1	1	1	1
murugan v	819687b	46	2	1	3	312	0	70	174	205	3712	12	1	2	1	1	1
murugesar	625084c	35	2	1	2	4	0	60	169	42	935	13	0.8	1	1	1	1
muthu n	434876c	34	2	1	4	24	0	52	174	.	480	11	0.8	1	1	1	1
muthusam	477615c	56	2	1	2	46	0	63	155	159	987	11	1	1	1	1	1

mylsamy	311378c	39	2	1	2	112	1	47	163	66	472	8.8	0.8	1	1	2	1
nagarathna	923657b	35	1	1	1	104	0	35	155	251	2576	12	0.8	1	1	1	1
nagendra p	447603c	30	2	1	3	54	0	52	169	111	1168	15	0.8	1	1	1	1
nageshwar	701882a	44	2	1	4	24	1	61	172	.	1100	13	1	2	1	4	1
nallusami	585420b	38	2	1	3	424	0	58	166	59	1161	12	0.9	2	2	3	1
narasimhul	357753c	35	2	1	3	104	0	50	160	173	1700	12	1	1	1	1	1
narasimha	288067c	28	2	1	4	156	0	64	169	63	1142	13	1	2	2	1	1
narasimha	488817c	36	2	1	3	8	0	64	163	50	870	11	1	1	1	1	1
natarajan	616678c	60	2	1	3	104	0	60	167	211	2376	13	0.9	1	1	2	1
natrayaswa	378221c	46	2	1	4	56	0	44	152	43	1056	12	0.9	1	1	1	1
nookaraju (	638105c	50	2	1	3	16	0	53	161	118	1078	13	0.9	1	1	2	1
pachaiyapp	177370b	50	2	1	3	28	0	58	171	50	896	9.2	1	2	2	1	1
padma	443633c	32	1	1	2	96	0	45	151	28	204	9	0.7	2	1	1	1
padm.j	955826b	34	1	1	4	208	0	38	145	241	3034	9.7	1	1	1	1	1
padmanath	185377c	48	2	1	4	260	0	67	165	48	720	14	1	2	2	1	1
palani m	702111b	31	2	1	4	156	0	42	154	.	549	12	0.9	.	.	1	1
palani r	059814c	50	2	1	4	208	0	70	172	16	388	8.1	1	2	1	1	1
palaniamm	487453c	52	1	1	3	20	0	50	154	73	1157	9.8	0.9	1	1	1	1
palaniappa	540732c	70	2	1	3	4	0	52	174	50	1300	10	1	1	1	1	1
paneer sel	461305c	50	2	1	4	4	0	69	174	130	2108	14	0.9	1	1	4	1
pandiyarjar	301655c	40	2	1	3	32	0	66	156	171	1911	13	1	1	1	1	1
pandurang	385372c	38	2	1	4	52	0	40	163	273	1500	10	1	1	1	1	1
parthasarth	512137c	38	2	1	3	16	0	57	167	166	1108	12	0.8	1	1	2	1
pasala bala	888167b	34	2	1	4	260	0	57	163	.	312	8.1	1	1	1	1	1
patricia	184228c	43	1	1	4	104	0	35	153	61	432	7.9	0.9	1	1	1	1
pedda subl	262333c	58	2	1	3	26	0	59	164	117	1404	11	1	2	2	1	1
periyaswar	708349c	70	2	1	3	4	0	62	168	272	1425	13	1	1	1	4	1
pramila	512288c	58	1	1	3	58	0	70	159	120	1098	12	1	1	1	4	1
prathap rec	566354c	43	2	1	1	27	0	41	167	69	689	8.2	0.8	1	1	4	1
radha kum	521374c	40	1	1	4	8	1	53	152	50	380	9.1	0.7	1	1	1	1
raghavendı	913764b	35	2	1	3	56	0	44	173	113	762	13	1	2	2	1	1
raghu.a	093135c	29	2	1	2	208	0	57	180	77	900	11	0.9	1	1	2	1
raja m	464301c	40	2	1	4	48	0	62	165	.	2528	13	1	1	1	1	1
raja r	582282c	40	2	1	3	20	0	47	169	129	1126	10	1	1	1	1	1
rajambal.v	236358c	61	2	1	2	12	1	50	152	166	2700	11	0.6	1	1	1	1
rajendran	523595c	43	2	1	4	8	0	65	178	102	1150	17	1	1	1	1	1

raju	365079c	40	2	1	4	46	0	51	167	.	1120	9.6	0.8	2	2	1	1
ramachanc	731875c	45	2	1	3	12	0	48	157	162	935	13	1	.	.	1	1
ramamurth	399251c	35	2	1	4	16	1	54	159	.	1140	14	0.8	2	2	1	1
rajamma	359673c	36	1	1	4	24	0	60	158	95	1105	12	0.8	1	1	1	1
ramanamm	422604c	24	1	1	3	104	0	45	152	57	750	8.1	.	2	2	1	1
ramanjulu	676019c	35	2	1	3	4	0	48	162	223	850	8.8	.	1	1	2	1
ramesh ba	523691c	32	2	1	3	4	0	40	157	260	1459	11	0.8	1	2	1	1
ranjith kum	475454c	47	2	1	4	32	0	45	150	.	2467	9.3	0.7	2	2	2	1
ravichandr	723306c	34	2	1	4	8	0	77	180	10	589	13	1	1	2	2	1
ravikumar	320286b	35	2	1	3	16	0	59	167	.	990	11	1	2	2	1	1
reddanna	725445c	50	2	1	3	8	0	44	153	48	920	9.9	1	2	1	1	1
reddappag	360626c	34	2	1	3	82	0	52	163	149	1110	12	0.8	1	1	1	1
reddyiah	509894c	33	2	1	2	12	0	57	172	264	1690	15	0.9	1	1	1	1
renuka.n	490752c	28	1	1	2	29	0	55	155	135	2421	11	0.6	1	1	2	1
sampath r	401667c	28	2	1	4	28	0	35	157	30	700	12	1	1	1	3	1
sankari m	691341c	36	1	1	3	12	0	61	159	32	1110	9.9	0.6	2	1	1	1
santosh	592656c	38	2	1	4	12	0	55	170	.	1090	11	1	1	1	2	1
saravanan	931243b	40	2	1	3	208	0	58	172	53	1123	12	1	1	1	1	1
saravanan	302819c	30	2	1	2	64	0	51	169	202	1476	13	0.9	1	1	1	1
saravanan	019805c	31	2	1	2	212	0	55	170	278	1188	10	0.9	1	1	1	1
sashikuma	557319c	28	2	1	3	208	0	84	174	311	1720	16	1	1	2	2	1
satish kum	494491c	31	2	1	2	52	0	59	168	157	324	8.8	0.8	1	1	4	1
satya teertl	294967c	44	2	2	2	24	0	56	164	233	3008	.	0.9	1	1	1	1
savithri	563289c	37	1	1	3	24	0	46	154	47	898	8.9	0.8	1	1	2	1
sekhar d r	192874c	34	2	1	3	104	0	65	170	268	1342	9	1	1	1	1	1
selvaraj c	654906c	45	2	1	4	18	0	55	169	63	320	7.9	1	2	2	3	1
selvaraj m	590584c	34	2	1	3	54	0	73	171	132	990	14	0.9	2	2	2	1
selvi s	210923b	42	1	1	4	520	0	38	149	.	1100	10	0.7	1	1	1	1
seranjivi t	503684c	34	1	1	3	18	0	60	164	212	1548	12	0.7	1	2	1	1
sethurama	674029c	57	2	1	3	10	0	50	152	92	1780	9.1	1	1	1	1	1
shankar r	256196b	36	2	1	4	208	0	60	168	.	480	11	1	2	1	1	1
shujath	746233c	36	2	1	4	4	0	65	173	136	1140	12	1	1	1	2	1
sibin mathe	977324b	30	2	1	3	208	0	54	162	.	1183	9.3	0.8	1	1	1	1
silambaras	195439c	25	2	1	4	156	0	43	159	33	989	9.7	0.8	1	1	1	1
siromani	262140c	42	1	1	3	104	0	60	163	62	780	14	0.7	1	1	1	2
sivakumar	458772c	34	2	1	3	24	0	76	174	62	.	.	.	.	.	1	1

sivakumar	183663c	40	2	1	3	52	0	58	161	83	1108	11	1	2	2	1	1
sivaprasad	564667c	36	2	1	4	4	0	51	160	92	1188	11	1	.	.	1	1
siva reddy	561188c	43	2	1	2	48	0	71	174	153	2160	14	0.8	1	1	1	1
sivasami s	654477c	37	2	1	4	6	2	45	164	30	680	13	0.9	2	2	1	1
soundarraj	031025c	36	2	1	4	156	0	40	164	.	1138	9.8	1	2	2	2	1
soundarraj	195236c	44	2	4	2	104	1	46	157	205	1640	8.9	0.8	1	1	1	1
sreenivasa	562093c	38	2	1	2	24	1	76	168	134	1148	11	1	2	1	1	1
srinivа rao	615559c	38	2	1	2	4	0	75	178	198	1060	12	1	1	1	2	1
sreenivasu	591773c	32	2	1	2	4	0	52	160	182	1090	13	0.9	1	1	1	1
stevenson	497967c	51	2	1	2	8	0	60	168	52	1332	11	0.8	1	1	3	1
subramani	434693b	47	2	1	2	106	4	55	164	182	2548	14	1	1	1	1	1
subramany	467205b	50	2	1	2	156	0	47	167	195	1582	14	0.9	1	1	1	1
subramani	542869c	42	2	1	4	8	0	54	165	65	1280	11	0.9	1	1	1	1
subramani	567746c	46	2	1	4	52	0	52	170	19	679	14	1	2	2	1	1
sujatha h	736678b	33	1	1	2	156	0	53	152	85	860	13	0.8	1	1	1	1
sujatha k	367149b	27	1	1	2	16	0	42	144	.	3220	12	0.8	1	1	1	1
sumathi k	937700b	29	1	1	3	104	0	41	156	.	1890	11	0.9	1	1	1	1
venkateswa	687708C	30	2	1	2	16	0	45	151	230	1212	12	0.8	1	1	1	1
sundara m	440385c	30	2	1	4	8	1	59	163	130	600	11	1	1	1	3	1
sundara va	470725c	40	2	1	2	48	0	60	168	168	866	14	0.7	1	1	1	1
sunil kuma	627481c	30	2	1	2	8	0	85	170	179	2520	14	1	1	1	1	1
surabhi sri	497237c	33	1	1	3	52	0	81	172	101	1530	14	1	1	1	2	1
surendrana	367446c	30	2	1	3	104	0	51	160	81	224	11	1	1	2	1	1
suresh g	446896c	34	2	1	3	4	0	44	162	33	600	7.9	0.7	2	1	3	1
suresh gup	201426b	35	2	1	3	314	0	53	163	134	800	15	0.9	1	1	2	1
suresh p	961202b	35	2	1	3	104	0	53	166	.	1061	10	0.8	1	1	3	1
surya	434041b	37	2	1	2	52	0	51	172	326	2816	13	1	1	1	1	1
selvi t	389318c	38	1	1	4	52	0	55	153	184	777	11	0.8	1	1	1	1
thangavel	638872c	34	2	1	3	4	0	47	164	41	1575	13	0.7	1	1	1	1
thavamani	080746c	49	1	1	3	53	1	67	156	.	1408	13	0.9	2	1	1	1
thirumalai r	631587c	40	2	1	4	54	0	69	166	49	1129	15	1	1	1	1	1
thirumalais	713509c	36	2	1	2	4	0	58	170	117	1190	14	1	1	1	1	1
thokuli	725480c	35	1	1	3	4	0	65	166	339	2040	12	1	2	2	4	1
uma s	931244b	29	1	1	4	208	0	51	153	103	769	7.9	0.6	2	1	3	1
uma gouri	571826c	36	1	1	2	48	0	64	160	261	1720	12	0.8	1	1	1	1
uma mahes	6423381	40	2	1	4	364	0	65	173	19	660	12	1	2	1	1	1

usha	649355a	36	1	1	2	260	0	51	159	225	2043	11	0.9	.	.	1	1
uthayasekh	459270c	41	2	1	3	24	0	55	163	50	1104	9.6	2	1	1	1	1
vaithinatha	651835c	42	2	1	2	8	2	60	173	296	1478	14	1	2	2	2	1
vanitha	713510c	26	1	1	3	4	0	37	156	56	780	11	0.6	2	2	1	1
vasudevan	597249c	29	2	1	3	24	4	46	159	74	1406	12	0.8	1	1	1	1
veni	589029c	45	1	1	3	4	0	58	152	101	1040	13	0.7	2	1	1	1
venkatesar	556682c	37	2	1	2	32	1	52	175	56	1402	11	0.8	1	1	2	1
venkatesha	475976c	43	2	1	3	44	0	52	167	101	2178	13	1	1	1	1	1
venkattamr	562298c	58	1	4	3	104	0	56	148	102	1115	11	0.7	1	1	2	1
venkata sa	140923c	31	1	1	3	156	0	61	156	126	789	12	0.7	2	2	1	1
venkatesw	554347c	56	2	1	3	4	0	37	158	60	320	12	0.7	1	1	3	1
victor a m	926618b	39	2	1	4	208	0	45	169	30	1020	16	1	1	1	1	1
vijaya	689876c	38	1	1	3	4	0	46	152	130	705	10	0.9	2	2	1	1
vijaykumar	434107c	53	2	1	3	52	1	57	168	49	720	9.6	1	2	1	3	1
balasubran	622642c	45	2	1	4	4	0	58	172	21	736	8.3	1	1	1	1	1

ATT	**end point**	**reason**	ADR	smoking	death	followup
2	**1**	**3**	0	1	1	4
2	**1**	**1**	4	1	1	36
2	**2**	**0**	0	2	1	52
1	**1**	**1**	3	2	1	7
2	**1**	**1**	5	1	1	20
2	**2**	**0**	0	2	1	64
2	**2**	**0**	0	2	1	52
2	**2**	**0**	0	1	1	76
2	**2**	**0**	0	2	1	48
2	**2**	**0**	0	2	1	56
2	**1**	**1**	5	1	1	22
2	**1**	**1**	5	1	1	54
2	**2**	**0**	0	2	1	14
2	**2**	**0**	0	1	1	48
2	**2**	**0**	0	2	1	88
2	**1**	**2**	0	1	2	24
2	**2**	**0**	0	1	1	52
2	**2**	**0**	0	2	1	52
1	**2**	**0**	0	2	1	96
1	**1**	**2**	0	1	2	24
2	**2**	**0**	0	1	1	48
2	**1**	**3**	0	1	.	8
2	**2**	**0**	0	2	1	48
2	**2**	**0**	0	2	1	28
2	**1**	**1**	1	2	2	2
2	**1**	**1**	5	2	1	30
1	**2**	**0**	0	2	1	28
1	**1**	**3**	0	2	.	4
2	**1**	**1**	5	1	1	56
2	**1**	**1**	3	1	1	4
2	**1**	**1**	1	2	1	2
2	**1**	**2**	0	2	1	52
1	**1**	**3**	0	1	.	4
2	**2**	**0**	0	2	1	48
2	**1**	**1**	5	1	1	52

2	**2**	**0**	0	2	1	56
2	**2**	**0**	0	2	1	48
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2	**2**	**0**	0	2	1	28
2	**1**	**1**	4	2	1	48
2	**2**	**0**	0	2	1	52
2	**2**	**0**	0	1	1	52
2	**1**	**1**	4	1	1	44
2	**2**	**0**	0	1	1	48
2	**1**	**3**	0	1	.	4
2	**2**	**0**	0	2	1	48
2	**2**	**0**	0	2	1	48
2	**2**	**0**	0	2	1	56
2	**1**	**1**	3	2	1	8
2	**2**	**0**	0	2	1	28
2	**2**	**0**	0	2	1	52
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2	**2**	**0**	0	1	1	48
1	**2**	**0**	0	1	1	52
2	**1**	**2**	0	1	1	6
1	**1**	**1**	4	2	1	64
2	**1**	**1**	3	2	1	16
2	**1**	**1**	3	1	1	36
2	**2**	**0**	0	2	1	32
2	**1**	**1**	4	1	1	40
2	**2**	**0**	0	2	1	48
2	**2**	**0**	0	2	1	52
2	**1**	**3**	0	1	.	4
2	**2**	**0**	0	2	1	32
2	**1**	**4**	0	1	2	4
2	**1**	**2**	0	2	1	3
2	**1**	**1**	5	2	1	24
2	**2**	**0**	0	2	1	32
2	**1**	**1**	5	2	1	48
2	**1**	**3**	0	1	.	9
2	**1**	**3**	0	1	.	4

1	**2**	**0**	0	2	1	52
2	**2**	**0**	0	2	1	68
2	**2**	**0**	0	2	1	28
1	**2**	**0**	0	2	1	32
2	**1**	**1**	6	2	1	32
2	**1**	**1**	4	2	1	36
1	**1**	**1**	3	2	1	4
2	**2**	**0**	0	1	1	52
2	**1**	**3**	0	2	.	2
2	**2**	**0**	0	2	1	52
2	**2**	**0**	0	2	1	48
2	**2**	**0**	0	2	1	52
2	**2**	**0**	0	2	1	52
1	**1**	**1**	4	2	1	56
2	**2**	**0**	0	1	1	52
2	**2**	**0**	0	2	1	56
2	**2**	**0**	0	1	1	44
2	**2**	**0**	0	1	1	84
2	**2**	**0**	0	2	1	24
2	**2**	**0**	0	2	1	68
2	**2**	**0**	0	2	1	56
2	**1**	**1**	1	2	1	2
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2	**1**	**1**	3	2	1	8
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2	**2**	**0**	0	2	1	28
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2	**1**	**3**	0	1	.	4
2	**2**	**0**	0	1	1	48
2	**2**	**0**	0	2	1	48
2	**2**	**0**	0	2	1	84
2	**2**	**0**	0	2	1	52
2	**2**	**0**	0	2	1	44
2	**2**	**0**	0	2	1	52
2	**2**	**0**	0	1	.	96
2	**1**	**3**	0	1	.	4

2	**2**	**0**	0	1	1	32
2	**2**	**0**	0	2	1	48
2	**2**	**0**	0	2	1	98
1	**2**	**0**	0	2	1	56
1	**1**	**4**	0	1	2	12
2	**2**	**0**	0	2	1	48
2	**1**	**3**	0	1	1	4
2	**1**	**1**	4	1	1	51
2	**1**	**1**	3	1	1	9
2	**1**	**1**	4	1	1	67
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2	**1**	**1**	4	1	1	48
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2	**2**	**0**	0	2	1	34
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2	**1**	**1**	4	1	1	31
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2	**1**	**3**	0	2	.	12
2	**1**	**3**	0	1	.	8
2	**2**	**0**	0	1	1	46
2	**1**	**1**	1	1	1	6
2	**1**	**1**	3	2	1	16
2	**2**	**0**	0	2	1	48
2	**2**	**0**	0	2	1	28
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2	**2**	**0**	0	2	1	84
2	**2**	**0**	0	2	1	48
1	**1**	**3**	0	1	.	8
2	**2**	**0**	0	2	1	44
2	**2**	**0**	0	2	1	48
2	**2**	**0**	0	1	1	56
2	**2**	**0**	0	2	1	84
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2	**2**	**0**	0	2	1	54
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2	**1**	**2**	0	2	1	52
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2	**1**	**1**	1	2	1	2
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2	**2**	**0**	0	2	1	3
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2	**2**	**0**	0	2	1	28
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